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# THE EFFECTS OF PENICILLIN ADMINISTRATION ON MENSTRUAL AND OTHER SEXUAL CYCLE FUNCTIONS

BY

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Since penicillin became available for the treatment of bacterial infections the non-

Nevertheless, a number of minor importance

The These were more frequent obtaining success penicillin therapy, however for the present less common, and were *Veneral Diseases* described, in the majority paper for half-centuries unavoidably present shown This is a processed drug which soon to return to normal for the treatment

of this country has made untoward drug-sequelæ extremely rare, in our experience, with the exception of those related to the menstrual function

Early in our series of cases, alterations in the normal menstrual cycle of non-pregnant patients were observed, notably the onset of premature menstrual periods, lengthened periods, increased loss, and premenstrual or

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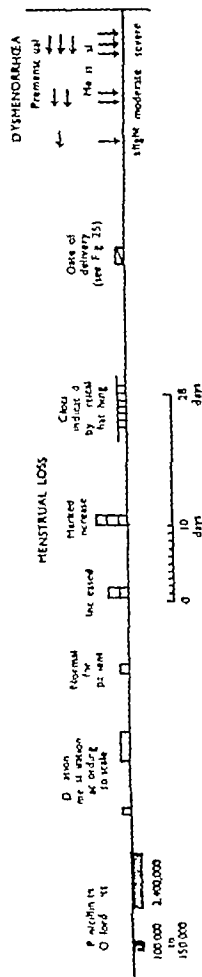
monatous vaginitis whose treatment had been completed These 3 patients were particularly chosen for their

previous constancy in menstrual cycle, loss, and dysmenorrhœa The results of the administration of 150 000 Oxford units of penicillin, given in 5 doses each of 30,000 units at 3-hourly intervals, are shown graphically in Figs 1, 2, 3 In one of the patients menstruation occurred 7 days before the expected date in the other two the periods were delayed by 7 and 10 days respectively The duration of menstrual flow was increased by 2 to 3 days in all 3 patients Loss was increased in all instances, and cramps were also increased in the 2 cases in which they normally occurred Premenstrual dysmenorrhœa was increased in one, abolished in one, and instituted in the third Menstrual dysmenorrhœa, severe in one patient, occurred for the first time in all 3 patients and persisted throughout the period In these cases the subsequent periods were normal in all respects This experiment indicated that menstrual irregularities could be instituted by the penicillin available, and it was decided to investigate the subject further

Examination of the literature has revealed few observations on the menstrual sequelæ of penicillin administration. Leavitt (1945) states "The effect of penicillin in inducing premature menstruation or in prolonging menstruation already started has been the subject of comment by several of the doctors contributing to the *Bulletin of the Rapid Treatment Centres*" Unfortunately we have not been able to obtain access to this publication In his personal series of cases, Leavitt found that 8 out of 21 pregnant patients treated with penicillin manifested symptoms of uterine activity—uterine cramps, bleeding,



## KEY TO SYMBOLS



Menstrual sequelæ of penicillin, normal controls, etc      Vertical lines indicate 28-day intervals

Fig. 1.—Normal control 150,000 units penicillin 11th day of cycle. Period advanced by 6 days, increased premenstrual dysmenorrhea, menstrual dysmenorrhea instituted, increased loss and clots.

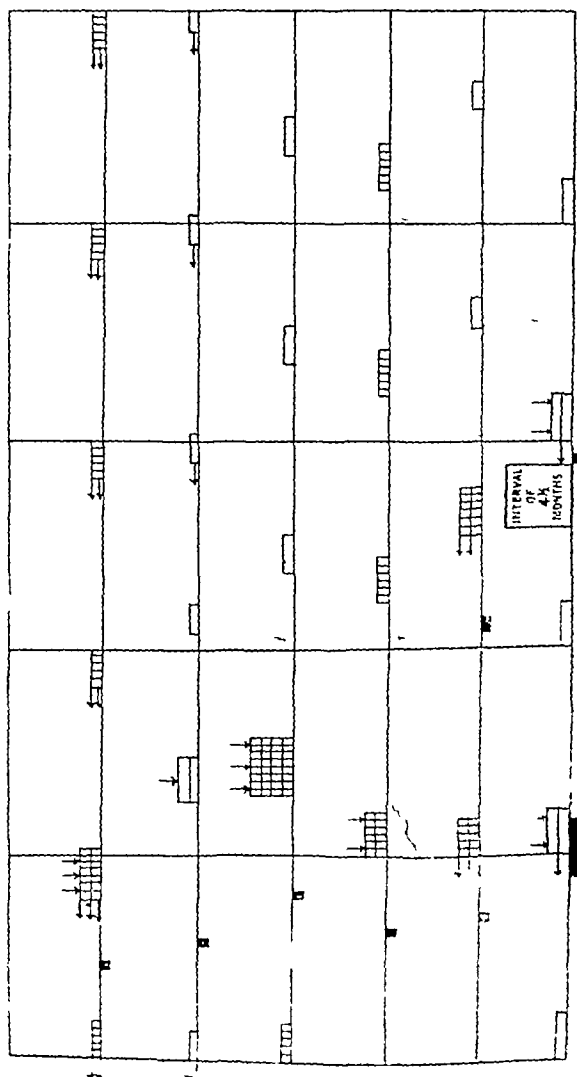
Fig. 2.—Normal control 150 000 units penicillin 16th day of cycle. Period delayed 7 days. Increased loss temporary abolition of premenstrual dysmenorrhoea, institution of menstrual dysmenorrhoea.

Fig. 3—Normal control 150 000 units penicillin 22nd day of cycle. Period delayed 8 days exceptionally severe menstrual dysmenorrhoea instituted, exceptionally heavy loss

Fig. 4—Physiological amenorrhoea (3 months duration) 150,000 units penicillin menstruation re-instituted 9 days later increased loss temporary menstrual dysmenorrhoea

Fig 5.—Physiological amenorrhoea 150 000 units penicillin, 7 days later menstruation re-instituted heavy loss premenstrual dysmenorrhoea instituted Similar phenomena after 640,000 units 38 days later, followed by normal cycle

Fig 6.—Repeated administration of penicillin similar to menstrual sequele following 2,400 000 units and 150,000 units at interval of over 6 months



or both. Of these 8 patients, 2 evacuated the contents of the uterus. He considered that the action of the penicillin on the uterus might be due to some impurity, as 7 of these 8 cases had been treated with the same batch of the drug. Lentz and others (1944) noted 2 cases of threatened abortion following penicillin treatment for syphilis in pregnant women. Mascall (1945) stated that almost all his patients complained of premenstrual pain or uterine pain, menorrhagia was a marked symptom, and if the period was nearly due its onset was expedited. In 2 cases of early pregnancy there had been abortion. He believed that these side-effects were due, not to the penicillin, but to some associated impurities. Walker (1945) had also noted similar menstrual phenomena.

Speiser and others (1946) did not observe any menstrual abnormality following penicillin therapy attributable to the drug. In only 1 instance in 100 cases of early syphilis treated with penicillin was there any alteration from the usual cycle. He suggested that some associated pathological process may have accounted for the intermenstrual bleeding noted by other workers. (This, in view of our recent observations with pure penicillin, may

be a reflex of the purity of the drug used by Speiser and others.)

### Personal Observations

The immediate and later sexual-cycle side-effects of penicillin administration have been studied in an unselected series of 216 non-pregnant women observed, except where otherwise indicated, for a minimum of 4 post-therapeutic menstrual cycles, in 32 pregnant women treated at varying stages of gestation, and in 16 women whose treatment commenced during the puerperium. Sodium and calcium salts of varying batches and of different manufacture have been employed in aqueous solution, or in beeswax-arachis-oil or beeswax-ethyl-oleate emulsion. There has been insufficient evidence to indicate that any individual batch of drug or vehicle was more—or less—provocative of reactions than the others. On the other hand it is apparent from consideration of the graphs that, while the sequelæ were minimal in patients treated with 100,000 Oxford units (Figs 7 to 10), these are of essentially similar character to those occurring in the higher dosage groups (Figs 11 to 21). The distribution of cases, schemes of penicillin treatment, and incidence of uterine sequelæ are indicated in Table I.

TABLE I

PENICILLIN DOSAGE AND INCIDENCE OF UTERINE SEQUELÆ

Total dosage of penicillin	100 000 units			150 000 units			200 000 units			300 000 units			2,400 000 units			2,400,000 units			Total
Details of administration and salts used	5 × 20 000 units 3-hourly (aqueous solution) sodium			5 × 30 000 units 3 hourly (aqueous solution) sodium and calcium			single dose (emulsion) calcium			single dose (emulsion) calcium			40 000 units 3-hourly for 7½ days (aqueous solution) sodium and calcium			single dose 300 000 units daily for 8 days (emulsion) calcium			
	No of patients	No affected	% affected	No of patients	No affected	% affected	No of patients	No affected	% affected	No of patients	No affected	% affected	No of patients	No affected	% affected	No of patients	No affected	% affected	
Non pregnant	8	6	75.0	42	40	95.2	46	34	73.9	4	4	100	96	94	97.9	10	10	100	
Pregnant	—	—	—	6	1	16.7	6	1	16.7	—	—	—	20	12	60.0	—	—	—	
Puerperal	—	—	—	4	2	50.0	—	—	—	—	—	—	12	10	83.3	—	—	—	
Amenorrhoea																			
Physiological (no cause ascertained)	4	4	100	—	—	—	—	—	—	—	—	—	2	2	100	—	—	—	
Pubertal	—	—	—	—	—	—	—	—	—	—	—	—	2	2	100	—	—	—	
Menopausal	—	—	—	—	—	—	—	—	—	—	—	—	2	2	100	—	—	—	
Normal controls	—	—	—	3	3	100	—	—	—	—	—	—	—	—	—	3	3	100	

### Typical menstrual sequelæ of penicillin, 100,000 units

Fig 7.—100 000 units penicillin 3rd day of cycle, followed by 2 heavy periods at expected dates

Fig 8.—100 000 units penicillin 18th day of cycle, period advanced 7 days, 21 days duration

Fig 9.—100 000 units penicillin 25th day of cycle, period advanced 3 days—lengthened by 6 days, subsequently normal cycle

Fig 10.—100 000 units penicillin 25th day of cycle, period advanced 3 days, clots instituted, subsequent periods normal

### Menstrual sequelæ of penicillin, 150,000 units

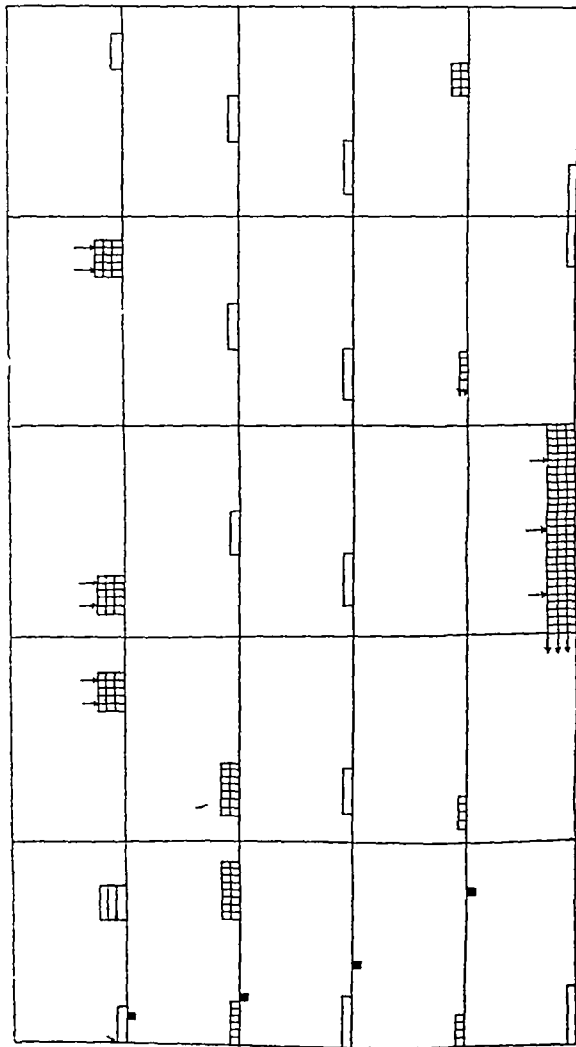
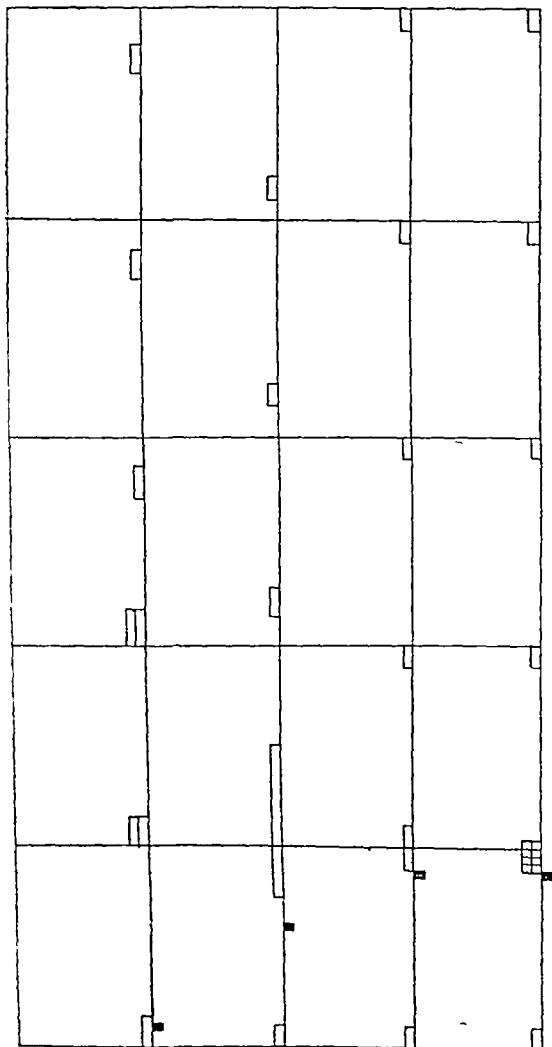
Fig 11.—150,000 units penicillin 4th day of cycle, period advanced 10 days, heavy loss. Similar heavy periods at intervals of 28 days 13 days 45 days. Clots and severe menstrual dysmenorrhœa instituted. Subsequent periods normal

Fig 12.—150 000 units penicillin 7th day of cycle, period advanced 10 days, increased loss, clots and duration. Period 14 days later, similar type. Subsequent periods normal

Fig 13.—150 000 units penicillin 11th day of cycle, period delayed 3 days, normal

Fig 14.—150 000 units penicillin 22nd day cycle. Normal period 7 days later, 55 days later, period with institution of premenstrual dysmenorrhœa, 40 days later, heavy period with clots

Fig 15.—150 000 units penicillin 29th day of cycle, 28 days later very heavy period, 28 days duration. Premenstrual and menstrual dysmenorrhœa instituted. Next period 21 days later, 14 days duration. No further record



# Menstrual sequelae of penicillin, 2,400,000 units

Fig 16 —2,400,000 units penicillin 11th day et seq of cycle  
Very heavy period at normal date Increased duration  
Institution of clots and marked menstrual dysmenorrhea;  
heavy periods with clots and menstrual dysmenorrhea;  
20 and 42 days later subsequent periods showed per-  
sistence of increased loss, clots and pain

Fig 17 —2,400,000 units penicillin 17th day et seq of  
cycle Heavy period at normal date subsequent periods  
normal

Fig 18 —2,400,000 units penicillin at 21st day et seq of  
cycle Heavy period delayed 7 days increased pre-  
menstrual and institution of menstrual dysmenorrhea  
and clots normal period 23 days later

Fig 19 —2,400,000 units penicillin at 24th day et seq of  
cycle Normal period 8 days late

Fig 20 —2,400,000 units penicillin at 26th day of cycle  
Shortened period delayed 8 days 28 days later heavy  
lengthened period with institution of clots subsequent  
periods heavy with clots

Fig 21 —2,400,000 units penicillin at 30th day et seq  
of cycle Heavy lengthened period delayed 6 days, clots  
instituted 21 days later heavy period with clots, men-  
strual dysmenorrhea instituted Normal cycle after 5th  
month

# Menstrual sequelae of penicillin, menarche, menopause

Fig 22 —Menarche aged 14½ No period for 6 months  
2,400,000 units penicillin period commenced 2nd day  
lasted 4 days 32 days later similar period Transferred—  
no further data available

Fig 23 —Menopause aged 51 No period for 9 months  
2,400,000 units penicillin 1 day loss on 3rd day of  
penicillin 22 days later heavy 4 day period 20 days  
later normal period No further periods occurred

Fig 24 —Menopause aged 45 Previous periods 86 and  
129 days before 2,400,000 units penicillin normal period  
7 days after completion, 40 days later 3 day period No  
further periods occurred

Fig 25 —2,400,000 units penicillin 37 days after delivery  
Heavy 4-day period 25 days later marked premenstrual  
dysmenorrhea periods at intervals of 25 28 28 days  
etc no interference with lactation

Fig 26 —150,000 units penicillin 17th day of cycle  
Heavy lengthened period 5 day early clots instituted  
thin scanty 1 day loss 3 and 6 days later very heavy  
5-day period with clots premenstrual and institution of  
marked menstrual dysmenorrhea Further 1 day losses  
at approximately 3-4 day intervals until next period  
17 days later subsequent periods normal

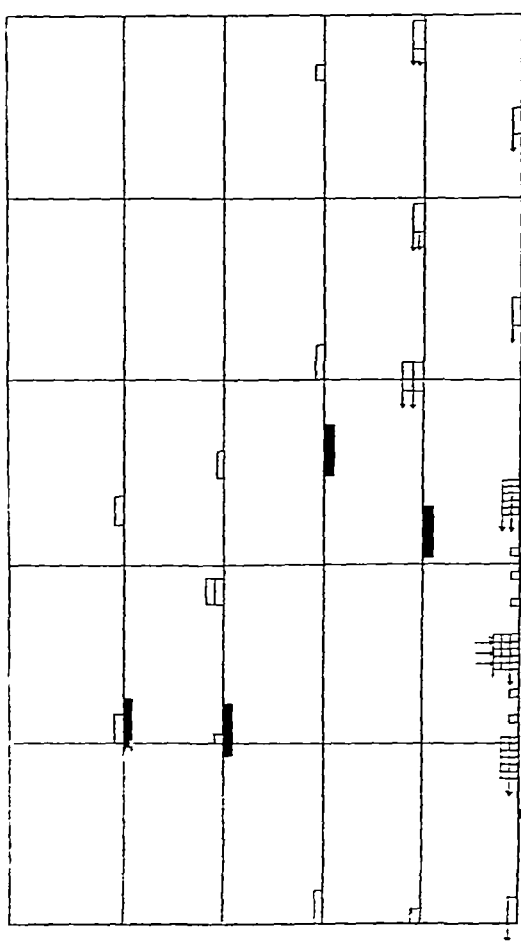
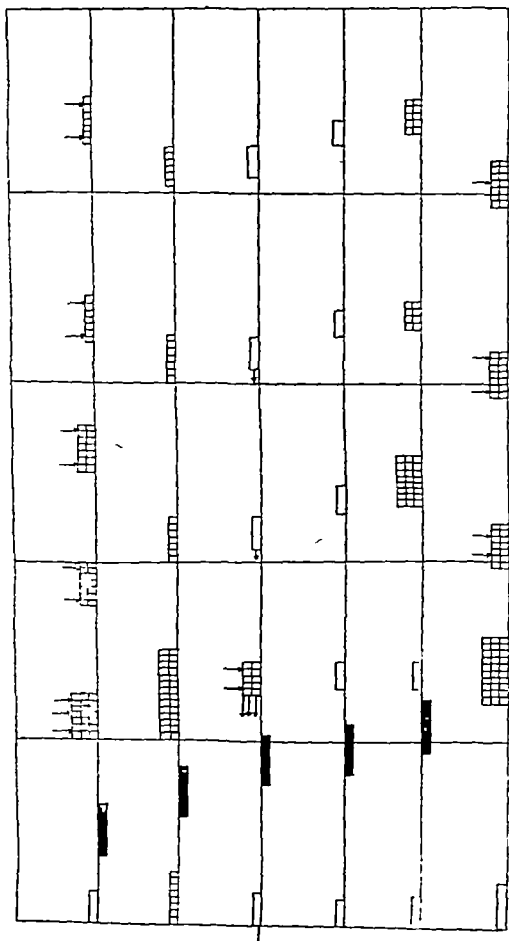


TABLE II

PENICILLIN DOSAGE AND MENSTRUAL PERIODS AFFECTED

Penicillin dosage in Oxford units	Number of patients	Number of patients affected	Post-penicillin menstrual periods affected			
			1	1, 2	1, 2, 3	1, 2, 3, 4
100,000	8	6	2	4	—	—
150,000	42	40	30	4	4	2
200,000	46	34	20	10	4	—
300,000	4	4	2	2	—	—
2,400,000	106	104	64	24	4	12
Total	206	188	118	44	12	14
Percentage	100	91.3	57.3	21.4	5.8	6.8

## MENSTRUAL FUNCTION SEQUELÆ

*Menstrual Periods*—Analysis of the menstrual periods affected in the various groups of patients (Table II) indicates that, in the vast majority, the sequelæ have been related to the first 2 post-penicillin cycles although in some cases the third and fourth cycles may also be affected. There is again a striking similarity in the pattern of results in the various groups independent of time-dosage factors.

The chief symptomatic changes in relation to the menstrual function are shown in Table III. Approximately 60% of the patients show changes in cycle, in duration of period, and in menstrual loss.

*Menstrual Cycle*—The cycle was lengthened in 27.2% of cases, the average increase being 9 to 11 days (limits, 2 to 41 days), it was shortened in 32.7% of cases, the average being 10 to 11 days (limits, 2 to 20 days). In the remaining 40.1% the cycles were unaffected.

*Menstrual Flow*—The duration of menstrual flow was lengthened in 44.5% of cases, the average increase being 5 to 6 days (limits, 1 to 22 days) beyond the patient's normal, it was shortened in 11.7%, the average being 2 days. The remaining 43.8% were unaffected.

*Menstrual Loss*—This was increased in 56.1% of cases, the increase in the majority being "marked," but in 10% being extremely heavy. Loss was decreased in 2.5% of cases, while the remaining 41.4% were unaffected. The occurrence of menstrual clotting for the first time was noted by 12.1% of patients.

*Dysmenorrhœa*—Perhaps the most striking feature of penicillin therapy has been the institution of premenstrual or menstrual dysmenorrhœa in approximately one-third of the cycles, while, on

the other hand, some 10% of patients normally suffering dysmenorrhœa experienced temporary or permanent relief. Premenstrual pain commonly occurred 2 days before the onset of flow, being of moderate severity in the majority of cases. Exceptionally, the associated abdominal pain and tenderness were hyperacute and were highly suggestive of an "acute abdomen." There were, however, no associated temperature, pulse rate, or respiratory increases, and the pain usually abated with the onset of menstrual flow. Menstrual pain, while usually of moderate degree in those affected, was occasionally of the utmost severity.

*Mittelschmerz Phenomenon*—The mittelschmerz phenomenon was noted in 8 patients, 6 of whom had had 2,400,000 units of penicillin for the treatment of early syphilis, the remaining 2 receiving 200,000 units for the treatment of gonorrhœa. None of these patients had previously experienced this phenomenon, nor has it recurred. One other patient complained of intermenstrual bleeding, she noted a scanty 1-day loss, recurring every third day for 2 menstrual cycles and commencing 3 days after the cessation of the first post-penicillin period (Fig. 26).

At the start of this investigation, an attempt was made to determine by graphical records whether a general pattern of results could be related to the time in the menstrual cycle at which penicillin was exhibited. It soon became apparent that the sequelæ—alterations in cycle, in loss, and in the occurrence of dysmenorrhœa, etc.—were unpredictable for any given patient. That, however, the sequelæ are of individual idiosyncratic pattern is shown in 5 of our cases by the recurrence of similar phenomena in the same patient on repeated administration of penicillin (Fig. 6).

TABLE III  
POST-PENICILLIN MENSTRUAL SEQUELÆ

	Penicillin dosage in Oxford units					Total	Per cent
	100,000	150 000	200 000	300 000	2.4 ml		
No of menstrual periods involved	12	60	64	6	182	324	100
<i>Menstrual cycle</i>							
Lengthened	2	18	12	0	56	88	27.2
Shortened	2	28	22	0	54	106	32.7
Unaffected	8	14	30	6	72	130	40.1
<i>Duration of period</i>							
Lengthened	6	26	22	6	84	144	44.5
Shortened	—	2	1	—	34	38	11.7
Unaffected	6	32	40	—	64	142	43.8
<i>Menstrual loss</i>							
Increased	10	46	30	4	92	182	56.1
Decreased	—	4	—	—	4	8	2.5
Unaffected	2	10	34	2	86	134	41.4
<i>CLOTS</i>							
Increased	—	12	2	—	6	20	6.1
Decreased	—	2	—	—	4	6	1.9
Instituted	—	12	6	—	22	40	12.4
Abolished	—	—	2	—	—	2	0.6
Unaffected	12	34	54	6	150	256	79.0
<i>Dysmenorrhœa</i>							
<i>Premenstrual</i>							
Increased	—	6	—	2	6	14	4.3
Decreased	—	2	—	—	—	2	0.6
Instituted	—	6	4	—	20	30	9.3
Abolished	—	2	2	2	12	18	5.5
Unaffected	12	44	58	2	144	260	80.3
<i>Menstrual</i>							
Increased	—	6	—	—	—	6	1.9
Decreased	—	2	—	—	2	4	1.2
Instituted	—	20	6	4	36	66	20.4
Abolished	—	4	—	—	8	12	3.6
Unaffected	12	28	58	2	136	236	72.9

#### PHYSIOLOGICAL AMENORRHOEA

In 3 cases of physiological amenorrhœa, varying in duration from 8 to 15 weeks and for which no cause could be determined 100,000 units of penicillin (for gonorrhœa) restored normal menstrual function. In the fourth case (of 3 months duration) a heavy period occurred 1 week after 100,000 units of penicillin, some 30 days later 640,000 units of penicillin were administered in 2 days for a relapse manifested by arthritis. This treatment was again followed by one heavy period, and subsequently by normal cycles (Figs 4, 5). In the other 2 cases of approximately similar durations, courses of 2,400,000 units for sero-negative primary and sero-positive syphilis were followed by the

same result. In 2 cases of pubertal amenorrhœa of 4 and 6 months' duration respectively, occurring in patients of 14 and 14½ years of age who were the subjects of congenital and acquired syphilis and who were treated with 2,400,000 units of penicillin menstruation was re-established for 2 complete menstrual cycles. Further follow up of these cases proved impracticable because of their transfer elsewhere (Fig 22).

#### MENOPAUSE

In 2 patients at the menopause penicillin temporarily restored the menstrual function. In 1 patient, aged 51 in whom no menstrual loss had been noted for 9 months, a 1-day flow occurred

on the third day of a 7½-day (2,400,000 unit) course of penicillin. This was followed 22 days later by a 4-day period of moderately heavy loss. No further menstruation was noted. The other patient, aged 45, had been increasingly irregular for about a year, the last menstrual losses being 86 and 129 days respectively before the commencement of a 2,400,000 unit course of penicillin for late syphilis. Seven days after completion of penicillin therapy a normal 6-day menstrual loss was experienced. This was followed by a 3-day loss 40 days later, since when the menses have ceased completely (Figs 23 and 24).

#### PREGNANCY

Of 32 cases of pregnancy treated with penicillin (Table IV), 12 experienced uterine cramps. Of this number 3 showed, in addition, uterine hæmorrhage. Cramps occurred most commonly on the first day, usually after the second or third injection

of penicillin, and consisted of a series of 1 to 3 moderately vigorous uterine contractions, followed by a sequence variable in number and gradually decreasing in amplitude. The contractions lasted over a period varying from a few minutes up to 2 to 3 hours. Recurrence of the pains was unusual. Bleeding was in no case of serious import, and varied from a slight staining of the linen to marked soiling of a sanitary pad.

Labour occurred in 5 patients, 3 between the seventh and ninth months of gestation, and the remaining 2 at "term". In the 3 patients of the first group (seventh to ninth month) labour pains followed "penicillin cramps" without any initial hæmorrhage. In 1 patient (7 months pregnant, in whom asymptomatic early syphilis was detected by routine ante-natal serological tests) the uterine cramps, of very moderate severity, began on the first day of penicillin treatment, passed off in 1½ hours, and were followed after an interval of

TABLE IV

PENICILLIN DOSAGE AND INCIDENCE OF UTERINE SEQUELÆ IN PREGNANCY

Month of pregnancy	Dosage of penicillin (Oxford units)	Number of patients	Uterine sequelæ						Day of onset of sequelæ (from commencement of injections)
			Uterine cramps		Bleeding *		Labour		
			No of patients affected	% affected	No of patients affected	% affected	No of patients affected	% affected	
0—3	150,000	2	1	50	1	50	—	—	5
	200,000	2	—	—	—	—	—	—	—
	2,400,000	2	—	—	—	—	—	—	—
4—6	150,000	—	—	—	—	—	—	—	—
	200,000	4	—	—	—	—	—	—	—
	2,400,000	6	2	33.3	1	16.7	—	—	1, 4
7—9	150,000	4	1	25	1	25	—	—	—
	200,000	—	—	—	—	—	—	—	—
	2,400,000	10	7	70	1	10	3	30	1, 1, 2, 3, 4, 6, 8
Term †	150,000	—	—	—	—	—	—	—	—
	200,000	—	—	—	—	—	—	—	—
	2,400,000	2	2	100	—	—	2	100	1, 8
		32	13	40.6	4	12.5	5	15.6	—

\* Bleeding was associated with uterine cramps and these cases are included in this group.

† Patients whose treatment began within 24 hours of the calculated date of confinement.

4 hours by labour pains. A macerated fœtus was expelled some 10 hours later. In this case for 4 or 5 days before the onset of labour fœtal movements had not been felt nor the fœtal heart sounds detected and the appearance of the fœtus was consistent with death at that time.

The second patient was suffering from late congenital syphilis, also detected by ante-natal serological tests. Uterine cramps of moderate severity began 2 hours after completion of the 7½ days course of treatment and persisted for 8 to 10 hours. Labour, which began the following day, resulted in a healthy 7 months' infant.

In the third patient, 8 months pregnant and the subject of untreated late secondary syphilis, fœtal movements ceased on the third day of penicillin treatment and the fœtal heart sounds could no longer be heard. Uterine cramps occurred on the third and fourth days but were of very mild character. Apart from this the course of penicillin was completed uneventfully. Thirty-six hours later labour commenced and resulted in the birth of a small macerated fœtus.

The role of penicillin in causing labour must be regarded as doubtful in the first and third cases, because of the fœtal death due to syphilis, but it cannot be ignored as a probable precipitant of labour in the second case. In the 2 cases at "term" i.e. within 48 hours of calculated date, labour commenced in 1 following uterine cramps consequent on the second penicillin injection, and in the other following cramps occurring on the last day of the course of treatment. From these cases at term no conclusions can be drawn. It seems, however, permissible to suggest that the sequelæ of penicillin treatment in pregnancy are more likely to occur with the higher dosages and in the more advanced stages of pregnancy.

#### PUERPERIUM

Of 16 patients whose penicillin treatment began early in the puerperium 12 showed some alteration in the lochia. Four patients were treated with 150 000 units. Of these 2, treated on the fifth and eleventh days respectively, were unaffected, 1 (fourth day) showed a marked increase in lochia rubra persisting for 36 hours which then rapidly diminished and became serous. 1 (eleventh day) showed a rapid diminution in lochia alba which had completely ceased at the termination of the 12-hours' penicillin administration. No further visible loss was reported.

Twelve patients were treated with 2,400,000 units. Two were completely unaffected. Three,

after penicillin commencing on the fourth, fifth, and eighth days of the puerperium respectively, showed a marked increase in loss, temporary in nature, and in no case persisting after the termination of the penicillin course or altering the normal sequence of lochial changes. Six (third, fourth, fourth, sixth, seventh, and tenth days respectively) experienced marked decrease of lochial flow without alteration of the total duration. In 1 patient (sixth day) however, the lochia ceased completely within 12 hours of the commencement of the penicillin course and did not become re-established.

#### LACTATION

During the puerperium it was noted that changes in lactation occurred in relation to penicillin therapy. Of the 4 patients treated with 150 000 units, 2 were unaffected, 1 showed a temporary decrease of secretion for 48 hours after penicillin administration, while 1, after a progressive diminution in secretion became "dry" after 5 days in spite of all efforts to restore the function. Of the 12 patients treated with 2,400 000 units 2 showed no lactatory changes, and 8 experienced a temporary decrease limited to the duration of penicillin administration. In 2 cases, however, lactation completely ceased and could not be re-established. Two of the 3 patients exhibiting failure of lactation had, in previous pregnancies successfully breast fed their infants.

The vagary of lochial alterations does not appear to depend upon the dosage or point in the puerperium at which the penicillin therapy was commenced. Similarly the stage of disease had no bearing, the 4 cases of gonorrhœa (150,000 units) were all uncomplicated, while analysis of the syphilis group shows no significant variations in sequelæ in the early, late, and late congenital stages. The numbers of cases observed are, however, so small that only the most tentative conclusions can be drawn.

In regard to lactation, however, a more constant sequel is seen in the depression of the function in 75 per cent. of the patients observed the criterion of 'decrease' being the necessity for the institution of supplementary feeding. Of those affected, 25 per cent. permanently ceased to lactate. Apart from the penicillin no extraneous factors could be elicited, and it seems not unreasonable to conclude that the drug was the inhibiting agent. No constant relationship was noted between the occurrence or type of lochial sequelæ and the diminution of lactation.



Our observations on patients treated later in the puerperium or during the normal lactation period are few, numbering only 3 cases, and are not included in Table I. In 1 case a course of 2,400,000 units, begun on the twenty-fourth day after delivery for late asymptomatic syphilis, resulted in a marked decrease of lactation during the 7½ days of treatment, and supplementary feeding had to be instituted. This measure became unnecessary within 48 hours of the termination of penicillin injections. In a second case of late congenital syphilis, treated from the twenty-eighth day as an out patient with daily injections of penicillin in oil-wax emulsion, no lactatory changes were reported. One-day menstrual losses, however, occurred on the thirty-third, forty-first, and forty-eighth days, no local cause could be detected, and no further losses were reported. In the third patient (late syphilis, 2,400,000 units in oil-wax emulsion) treatment was begun at the fifty-seventh day, no lactatory changes were reported, but a normal-duration heavy menstrual period with marked, unaccustomed premenstrual pain occurred 17 days after completion of drug therapy, in this case menstruation continued at normal intervals without change in lactation (Fig. 25).

### Summary and Conclusions

Menstrual cycle sequelæ were found to occur in 91.3 per cent of 206 non-pregnant female patients treated with penicillin in varying time-dosage schedules. The principal changes noted were alteration (lengthening or shortening) of the cycle and duration of flow, and the institution of premenstrual or menstrual dysmenorrhœa, occasionally of the utmost severity.

Uterine bleeding and/or cramps occurred in 43.8 per cent of 32 women at varying stages of pregnancy who were undergoing penicillin therapy, in 1 of these cases it is probable that this form of treatment precipitated the onset of labour at the seventh month.

Alterations in the lochia were observed in

75 per cent of 16 women treated during the first fortnight of the puerperium. Increased loss during the period of drug-therapy was seen in 4, decrease in 7, and complete ablation in 1.

Lactation was diminished in 75 per cent of 16 cases. While this decrease was usually limited to the injection period and normal function was subsequently rapidly regained, permanent cessation of lactation occurred in 25 per cent of those affected.

Restoration of normal menstrual function was noted in 1 patient treated late in the puerperium, a normal cycle becoming established without interference with lactation.

Reactions to penicillin cannot be forecast. They appear to result from individual idiosyncrasy, as is evidenced by the recurrence of a similar pattern of sequelæ on re-exhibition of the drug.

It is believed that these phenomena are caused by the penicillin available to us or to the impurities inseparable from the process of manufacture. That the latter hypothesis is the case is suggested by the decreasing frequency in recent months of such reactions, despite greatly increased penicillin dosage, and by the absence of sequelæ in 2 patients treated with pure penicillin.

We desire to express our thanks to the nursing staff of Q Ward, Southmead Hospital, whose co-operation has made the collection of data easier, and to the Medical Officer of Health of Bristol for permission to publish these observations.

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# COMMERCIAL-PENICILLINS AND THE TREATMENT OF SYPHILIS SOME RECENT AMERICAN DEVELOPMENTS

BY -

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On Feb 6 and 7, 1946, the United States Public Health Service convened a meeting of penicillin investigators of the National Research Council to set forth the latest developments in the treatment of syphilis with penicillin (Willcox, 1946). Included in the data presented was that of the cumulative experience of the treating of over 11,500 cases of early syphilis. Much of the work which was described has since appeared in the American medical press, culminating with the issue of the *Journal of the American Medical Association* of May 25, 1946. This issue also contained a most important statement by the Committee of Medical Research of the United States Public Health Service and Food and Drug Administration (1946).

Within a week of that meeting, information came to light from two different laboratories (of Dr Chesney and Dr Mahoney, who were working on the value of the different fractions of penicillin in experimental syphilis) that relapses were occurring as often with 10 times the dose of penicillin K as with penicillin G. Shortly after this, two widely separated clinics reported the paradoxical result that a schedule of a given dose over a given time was showing better results than another giving double the dose over double the time the latter treatment having been done at a later date than the former. Enquiries then showed that commercial penicillin furnished originally in June, 1943, and for some months afterwards, had consisted predominantly of G, in 1944, as a result of technicalities in its manufacture, it contained about equal parts of G, F, and K, whereas in 1945, in that produced by some manufacturers, K was predominant.

Conference in March, 1946

In this unexpected state of turmoil it was decided to hold a further conference on penicillin in which were represented the United States Public Health Service, the Food and Drug Administration, and the National Research Council. The conference was held at the surprisingly early date of March 26 and 27, 1946, at Washington, D C and was attended by over 150 interested medical men. This meeting, as in the case of the former one, was presided over by Dr J E Moore, and much extremely interesting material was presented.

## Experience of Research Workers

The first speakers were research workers, who indicated their experience with the various penicillin fractions. Following the reports from Dr Chesney and Dr Mahoney, studies had been done on blood and urine assays of the various fractions in rabbits and in man. For these experiments all workers had been able to use crystalline G and crystalline X penicillins, and penicillins containing 90 per cent. of K and 90 per cent. of F.

Dr H Eagle (Johns Hopkins Hospital) said that in rabbits the blood levels produced by injections of K were markedly lower than those by the other penicillins and similarly the concentrations produced were sustained over a shorter period of time. X gave higher levels than the others did, and for longer durations of time. Experiments on humans with G and K had shown a fourfold difference in the blood levels one hour after injection in favour of G, while the effect of G persisted for double the time. If as it might seem, K differed pharmacologically from the other three penicillins in that it was apparently destroyed

*in vivo* (disappearing from the blood faster than the others and not being recoverable to the same degree in the urine), it could then be anticipated that it would be less active not only in syphilis but in any infection. It was estimated that against the streptococcus penicillin K was only one-seventeenth as active *in vivo* as it was estimated it would be *in vitro*, and therefore some better method of ascertaining therapeutic activity should be adopted than that of estimating the bactericidal potency *in vitro*. As penicillin K was relatively inactive from the pharmacological standpoint rather than from its lack of activity *in vitro*, there might be wide discrepancies in the unitage contents of ampoules of commercial penicillins when these were based upon *in vitro* assays.

Dr Walsh McDermott (New York Hospital) had also made blood and urine assays on humans receiving the various fractions. He found that the penicillin concentrations in blood and urine following the administrations of crystalline G were essentially the same as for the current commercial penicillins. Values for crystalline X were also the same when the staphylococcus was used as the test organism, but were significantly greater when the streptococcus were employed. K was markedly inefficient in producing a blood concentration, and, in contrast to all other penicillins, detectable amounts could not be found in the blood 1 hour after it had been given.

Dr Coghill (Abbott Laboratories) had found that in humans there were significant levels of penicillin G after 2 hours, where with K only one out of four showed detectable levels in 45 minutes. Work on urinary excretion showed that penicillin G and penicillin X were relatively stable in the body, whereas penicillin K was quite unstable and only a small amount remained long enough in the blood for it to be excreted. The current Abbott penicillin contained 92 per cent G and 8 per cent K and gave apparently the same results as for penicillin G. Mixing G and K with pooled sera from 8 subjects did not seem to indicate that anti-penicillin substances in the blood were responsible for the rapid disintegration of penicillin K.

Dr Gladys Hobby (Charles Pfizer and Co.) who had been working on the relative values of the penicillin fractions, described results based on over 2,000 mouse-protection tests using a hæmolytic streptococcus. She considered from these tests that penicillin X was about half as effective as crystalline G. The amount of K required was about twice that of G, because the former was eliminated from the blood stream extremely rapidly.

Dr Justin Hill (Johns Hopkins University) presented data of *in vitro* work with the gonococcus which indicated that against this organism X was

superior to F, and F superior to G, G and K were graded at about the same level of activity.

### Clinical Reports

At this stage the meeting turned to the clinical side, and the chairman, Dr J E Moore, summarized the events that had led up to the conference. He stated that, in view of what had occurred, the central statistical unit had analysed further some of the material presented at the February meeting in respect of the time factor and had found a significantly higher relapse rate in patients treated for syphilis after May, 1944, than in those treated before that date, moreover, whereas the percentage becoming sero-negative at 11 months was 87 per cent before that date, it had dropped to 62 per cent afterwards.

Apart from the changes in the relative fractions in the penicillin already described, the potency of the penicillin obtained had varied from 220 units per mg in 1943, to 900-1,200 units per mg in its current form, and, therefore, it was likely that impurities had been removed. It had already been suggested that these impurities might contain anti-spirochætal substances (Dunham and Rake, 1945). Information was not available about what proportions of penicillin fractions G, F, X, and K were in the penicillins that had been employed in the treatment of syphilis, though batch samples were still held by the manufacturers and it might still be possible to determine such proportions. This, however, was not the only difficulty if the penicillin-syphilis data were to be adjusted, for it had also been discovered that the label dose of a bottle of penicillin signified its guaranteed minimum dose, and that there was no upper limit recorded of the maximum amount present.

Dr Perrin Long (Johns Hopkins University) also emphasized that previous published work on penicillin was influenced by the knowledge now available that an ampoule of penicillin might contain anything between 97,000 and 140,000 units. Latterly a check on the results in pneumonia had also shown that double the dose was required to produce the same clinical effect as formerly.

### Chemical Aspects of the Problem

At this stage, the meeting listened to the more chemical aspects of the problem, which it was hoped would show the way out from these sudden unexpected difficulties.

Dr Hans Clark (Columbia University) discussed the formulæ and chemical properties of the various fractions, and said that one would expect that

their affinity for water would increase from K through F and G to X, while their affinity for lipids would decrease from G through F and K to X. It was possible that one or other of these solubility properties might have a determining influence on the selective action on different organisms.

Dr F F Johnson (Cutter Laboratories) described an extraction method which caused a widely different distribution coefficient for each of the three penicillins G, F and K by means of which it was possible to separate three penicillins provided that it was known that only three antibiotics were present in the mixture. Dr Lyman Craig then discussed the possibilities of the counter current distribution method as applied to the identification of the penicillin fractions. This involved the use of a separator machine similar in principle to those used in the oil industry but much simplified.

### General Discussion

During the discussion that followed, the question of impurities was raised and Dr Clowes (Eli Lilly and Co) said it had been found that commercial penicillin would check the development of fertilized marine eggs but that the crystalline varieties would not do so. Even when the penicillins were removed the impurities still possessed this property. Dr Eagle said that he had used many penicillins of different potencies, but as far as animal syphilis was concerned there was little to be said about any effect of the impurities.

Further general discussion indicated that there were probably only 4 penicillins in all, that the respective amounts of the various fractions in commercial penicillins in the past 3 years were not known but probably could still be identified, that X was more stable than G in the bottle, and that the use of precursors or adjuvants in the production could modify the amount of G present and reduce that of K. If K were present in the penicillin then the total number of units per mg would be higher than without it. At this stage it became apparent that methods were known to the manufacturers which would increase the yield of the G content, and that several manufacturers had already adopted them. Hence, there was some confusion as to why the clinical results had fallen off, for although K had been indicted, it appeared to be almost absent from the current penicillins. It was suggested that a time lag

between discovery and performance was responsible for this. An advisory committee was set up to regulate further research in this important field, and the makers were being canvassed to find out what amounts of pure or nearly pure fractions they could make available for further study. It was then proposed and accepted by the meeting that it should be recommended that the grade of all penicillins should, as soon as possible, be labelled in milligrammes of penicillin and not in units.

### Events Subsequent to the Meeting

After this meeting events moved with extreme rapidity. It was learnt by early July (Moore) that many of the difficulties of manufacture had already been overcome, that practically all the commercial penicillin in the U.S.A. consisted predominantly of G, and that one firm had already placed on the market for commercial distribution a product containing 95 per cent. of G. It was anticipated that similar action by others would soon follow. Meanwhile research schedules under public health service auspices had switched to crystalline G.

Syphilis is one of the diseases in which, when studying the effects of penicillin, it is necessary to know with accuracy the dose that is being employed. Hitherto we have misled ourselves into believing we had a gauge of that accuracy, and as a result most of the previously published work about the effect of penicillin on syphilis has been rendered invalid. An exact study can begin only when a pure or practically pure substance is being used. When it was hoped that this stage had been reached in the United States, that country was, in time, considerably in advance of us, though even so it was still unlikely that worthwhile information would be forthcoming for 18 months. Since then, however, rumours have been circulating on both sides of the Atlantic that perhaps these penicillin fractions are not themselves the pure substances they were at first thought to be, and that many of the difficulties so far encountered may possibly be experienced again. Should this happen, British manufacturers may have the opportunity of catching up or even exceeding those of the U.S.A. in

furnishing a pure product for anti-syphilitic treatment

Another aspect of the problem is whether it will be possible to find a penicillin selective for the gonococcus which will not at the same time mask an incubating syphilitic infection. It has already been shown that penicillin X is more effective for acute gonorrhoea than commercial penicillin, but that X is less effective than G in causing the disappearance of treponemata from dark-field positive lesions. Preliminary tests, however, have not shown any indication that crystalline X at any rate might not mask a syphilitic infection (Olansky

and Putnam, 1946). Perhaps if further fractions are forthcoming this key, too, may be found

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# THE EVOLUTION OF SYPHILIS AFTER SMALL DOSES OF PENICILLIN A CRITICAL SURVEY

BY  
E CRONIN

The early work of Mahoney and others (1943) demonstrated that penicillin in doses of 60,000 to 100,000 units would produce rapid but temporary healing of primary syphilitic lesions. Even local applications of penicillin will destroy surface spirochaetes and may hinder the recognition of syphilitic disease (Cronin, 1946). What, so far, has not been adequately determined is whether 100,000 units of penicillin administered during the incubation period of syphilis delays the appearance of the primary chancre and a positive blood test, and, if they are so delayed, what reasonable period of surveillance is necessary to exclude their later occurrence. This problem is not restricted to venereal infection alone, but applies to any medical or surgical condition in which penicillin is used in similar amounts. How great is the risk of masking a syphilitic infection which may appear months or years hence? Can we ignore this risk completely, or is it necessary to subject our patients to interminable blood tests extending over an indefinite period of time?

The literature abounds with many personal opinions, but with little positive evidence. Canizares (1944) advises that patients who have received 100,000 units of penicillin for gonorrhoea should have blood tests done at intervals for 1 year "and preferably longer". Lydon and Cowe (1945) think a period of surveillance for 2 years is necessary. Allan (1946) urges blood tests during a period of 12 months. The administrative instructions in the British Army require a 6 months surveillance. Magnussen and Eagle (1945), basing their views on rabbit experiments, consider a minimum follow-up of 4 months to be essential. From this welter of contradictory statements, having little clinical data to support them and purely arbitrary in character, it is impossible to reach

any definite conclusion. One must examine the cases recorded to see what justification, if any, there is for these views.

In a previous communication (Cronin, 1945), 10 cases of gonococcal infection were reported which had been treated with 100 000 to 150,000 units of penicillin and in which syphilis subsequently developed without any intervening exposure. In all these cases a primary syphilitic lesion appeared within 3 months of treatment, associated with varied blood test results. Since then 19 further cases have been seen and the relevant details are given in Table I, which shows that 17 of these 19 cases developed a primary chancre and 1 a secondary syphilide within 3 months of penicillin therapy. One case of secondary syphilis occurred after this period.

## Discussion

Many apparent examples of the delay caused by penicillin in the appearance of syphilitic lesions have been reported. In several of them penile lesions were already present before penicillin administration, but they were either not seen, were undiagnosed, or were dark-ground negative. As was to be expected from the work of Mahoney and others already referred to, these lesions rapidly disappeared after penicillin therapy, but they either reappeared after an interval or else were succeeded by positive blood tests and secondary syphilides. These cases, while interesting and informative in showing that small doses of penicillin may alter the natural evolution of syphilitic disease, are not strictly germane to the immediate problem under discussion. The salient features are presented in Table II.

Some of the cases that remain have been excluded from further review. In case 2 of Ricchiuti's (1944) report, the diagnosis of

TABLE I

INCUBATION PERIOD AND STAGE OF SYPHILIS DEVELOPING AFTER THE TREATMENT OF GONORRHOEA WITH PENICILLIN (PERSONAL CASES)

Case No	Time in days from		Units of penicillin given	Probable incubation period in days	Kahn result	Clinical notes
	exposure to penicillin treatment	penicillin treatment to clinical lesion				
1	18	34	100,000	52	—	Primary chancre
2	13	36	100,000	49	—	Primary chancre
3	10	61	100,000	71	+++	Acute phimotic balanitis for preceding 2 weeks
4	15	35	100,000	50	+++	Primary chancre
5	3	36	100,000	39	+++	Primary chancre
6	5	36	150,000	41	—	Primary chancre
7	5	26	200,000	31	—	Primary chancre
8	10	142	100,000	152	++++	Maculo-papular syphilide (rash 3 weeks)
9	3	69	100,000	72	++++	Macular syphilide (scabies with non-healing penile ulcers 52 days after treatment)
10	5	61	100,000	66	+++	Primary chancre
11	9	16	100,000	25	—	Primary chancre
12	6	43	100,000	49	+	Primary chancre (ulcers of penis for 3 weeks)
13	6	39	100,000	45	—	Primary chancre
14	12	36	100,000	48	—	Primary chancre
15	5	41	100,000	46	—	Primary chancre
16	36	37	150,000	73	Doubtful	Primary chancre (non-healing chancroidal ulcers 1 week after treatment)
17	13	41	100,000	54	—	Primary chancre
18	27	55	60,000	82	+++	Primary chancre
19	5	10	100,000	15	+++	Primary chancre

TABLE II

RECRUDESCENCE OF SYPHILIS AFTER INITIAL INVOLUTION FOLLOWING PENICILLIN THERAPY FOR GONORRHEA

Time in days from			Units of penicillin given	Clinical notes	Authors
last exposure to penicillin treatment	penicillin treatment to clinical lesion	penicillin treatment to positive blood tests			
41	28	28	100 000	Ulcers of penis first appeared 22 days after exposure Blood tests and D G s negative	Hailey (1944)
32	23		50,000		Canizares (1944)
	57	57	100,000	Macular syphilide preceded by recurrence of penile ulcer for unknown period	Shafer and Zakon (1944)
		16	100,000		Ricchiuti (1944)
30	26	59	80,000		Boyd, Wagner, and Hewson (1944)
18	31	41	50 000		Carpenter (1944)
	35	35	80 000	Macular syphilide, recurrence of scrotal papule 14 days earlier	Walker and Barton (1945)
		10-14	125,000	Penile ulcer, D G negative after penicillin Did not heal	Van Slyke and Steinberg (1944)
		10-14	125,000	Penile ulcer, D G negative after penicillin Did not heal	Van Slyke and Steinberg (1944)
31		23-43	100 000		Bauer and Pincus (1944)
		10	125 000		Case 2 of Steinberg and Immergut (1945)



TABLE III

INCUBATION PERIOD AND STAGE OF SYPHILIS DEVELOPING AFTER THE TREATMENT OF GONORRHOEA WITH PENICILLIN (PREVIOUSLY REPORTED CASES)

Time in days from		Probable incubation period in days	Units of penicillin given	Clinical notes	Authors
last exposure to penicillin treatment	penicillin treatment to clinical lesion				
31	25	56	100,000	Maculo-papular syphilide Blood test positive	Atcheson (1945)
	33		100,000	Ulcer of frenulum	Van Horn and Dakin (1944)
	35		125,000	Primary chancre	Steinberg and Immergut (1945)
	49		125,000	Maculo-papular syphilide Blood test positive	Steinberg and Immergut (1945)
13	69	82	100,000	Penile ulcer appeared 51 days after treatment	Osmond (1945)
3	89	92	200,000	Primary chancre	Frankland (1946)
7	65	72	200,000	Primary chancre Blood test positive 5 days before positive D G	Batchelor, Donald, and Murrell (1946)
6	52	58	360,000	Primary chancre	Batchelor, Donald, and Murrell (1946)
5	72	77	200,000	Primary chancre	Batchelor, Donald, and Murrell (1946)
6	74	80	200,000	Seen 5 weeks later with florid secondary syphilis	Batchelor, Donald, and Murrell (1946)

syphilis, though suspected, was never confirmed. In the series by Batchelor and others (1946) 3 cases appear inadmissible. In case 1, after at least 700,000 units penicillin, they report, "First appearance noted of indurated sore at urinary meatus, and of a scar in the coronal sulcus". In case 2 penicillin was given on May 22, and yet on May 23 they observe, "Indurated lesion on under surface of penis". In view of the domestic complications involved in case 6, it is extremely unlikely that the patient's statement is reliable.

The remaining case reports in which no genital lesions existed prior to penicillin administration are presented in Table III. In most of these cases, clinical and serological evidence of syphilis appeared well within three months of penicillin therapy. In very few cases has there been unchallengeable proof of delay beyond this period, and in these cases penicillin in amounts of 200,000 units or more was given.

Although the apparent incubation period in all the cases, where obtainable, is very variable, what is of interest is the large number in which the appearance of the first clinical lesions occurred approximately 4 to 6 weeks after penicillin. One might be led to conclude that any spirochaetes remaining after penicillin therapy develop as though they were a fresh inoculum at that time. Magnusen and Eagle's (1945) work on experimental syphilis in rabbits gives some support for this view.

In a few cases, a syphilide appeared as the first clinical sign more than 3 months after treatment. There is no necessary causal relationship in this, for "syphilis d'emblée" is well-known, and many cases have been seen amongst troops who never received penicillin, and who are notoriously bad observers of genital lesions, especially when these are painless and hidden by the prepuce.

Finally, amongst many thousands of cases under post-penicillin surveillance for gonorrhoea, none have been seen in which blood tests negative at 3 months became positive at 6 months without there being either an intermediate exposure or a vaccine inoculation which would account for it. In these latter cases the serological test was weakly positive and variable.

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## Conclusions

There is no evidence that penicillin, in amounts up to 150,000 units, delays the appearance of syphilis for more than 3 months after treatment. Unnecessary psychological trauma and little benefit will accrue in extending surveillance beyond this period.

Where larger doses of penicillin are given, surveillance may require to be prolonged, but insufficient data is available to serve as a guide to its duration, since this is probably related to the amount of penicillin used.

Anyone administering penicillin, and particularly any practitioner assuming the responsibility of treating gonorrhoea with penicillin, should submit to careful examination any existing genital lesion, however little it may conform to the classical picture of a specific ulcer.

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# VENEREAL DISEASES IN THE BRITISH-OCCUPIED ZONE OF GERMANY\*

BY

F R CURTIS

Before discussing the situation with regard to venereal diseases in the British Zone of Germany after the end of hostilities in Europe, it is desirable to describe the situation before this date

## German Public Health Organization

Even before the Nazi régime the German organization had shown strong tendencies to increase the power of central government at the expense of local government, and this tendency was intensified by the Nazis. The German central government had no separate ministry of health, but all medical matters were controlled and directed by Department 4 of the Ministry of the Interior. The head of the department was usually a medical man, who, in matters of health, advised the Minister of Interior but had no direct access to the Cabinet. This department was responsible for far wider medical activities than the Ministry of Health in the United Kingdom. Not only public health, but medical associations, medical education, and the control of narcotics were functions of Department 4.

Below the central government, Germany was divided into states, such as Prussia, the governments of which formerly possessed considerable autonomy. These states, in turn, were divided into provinces, such as Schleswig-Holstein and Westphalia in the British Zone. These provinces were, as a rule, subdivided into government districts, which were again divided into local government areas called Kreise, some of which were urban and some rural. Each Kreis had a medical officer of health, who, in theory, had great powers and responsibilities, but, unlike his counterpart in the United Kingdom, he was not furnished with sufficient trained staff to carry out his tasks. For example, the medical officer of health had no sanitary inspectors and few health visitors. Much of the disposal of human excreta was farmed out to contractors, who in some parts of Germany handled 80 per cent of this work, but the collection and disposal went on with no

inspection by the medical officer of health. Further, the posts were not very well paid and did not, therefore, attract the best type of medical man.

Much of the work carried out in the United Kingdom by the staff of the medical officer of health was in Germany performed by the police. For example, there was a branch of the police called the Sanitary Police, whose training was frequently very sketchy and mostly on the apprenticeship basis. It was their responsibility to inspect and report on nuisances, restaurants, cafés, food, etc. Similarly, as we shall see, the police handled those problems in connexion with venereal disease which are dealt with in the United Kingdom by health visitors and social service workers.

## THE VENEREAL DISEASE PROBLEM

The German law as amended by Hitler's government clearly laid on the medical officer of health the responsibility for dealing with the venereal disease problem, but in fact very little of it was handled by him. The greater part of the total number of cases of venereal disease was treated by private practitioners, in either specialist or general practice. This situation was due to the widespread system of sickness insurance, which included between 80 and 90 per cent of the population, and to the fact that treatment of venereal disease was included in sickness insurance. Naturally, a small percentage of people drawn from the more well-to-do classes preferred to pay for their treatment, and these always consulted the specialist. On the other hand, there was a small percentage who either were not insured or not in benefit, and whose venereal disease treatment was a charge on public funds. These patients might still be treated privately or they might be referred to a hospital.

\* An address to the Medical Society for the Study of Venereal Diseases, October 26 1946

It is obvious that in such a system there was no incentive for central or local government to set up public clinics as has been done in the United Kingdom. Venereal disease cases could, if they wished, attend the out-patient departments of the university hospital or of the municipal hospitals in the large towns, but usually few chose to do so unless they developed complications for which hospitalization was a necessity.

In Germany there was no separation between the specialties of dermatology and venereal disease. To become a specialist in these subjects demanded four years' postgraduate training in one or more university hospitals. The training was intensive and extensive in the clinical and therapeutic aspects, but in relation to venereal disease there was a noticeable lack of attention to the public health aspect. Once a doctor had become a recognized specialist he might remain in his university town, holding a university appointment as well as practising privately, or he might set up in private practice in any large town, with or without a hospital appointment. In either case he would almost always be working essentially as a private individual not connected in any way with the local public health department.

Turning to the more technical aspects of venereal disease it is convenient to consider syphilis and gonorrhoea separately under the headings of diagnosis, treatment, and tests of cure.

### Syphilis

*Diagnosis*—Dark-field examination of serum obtained from chancres, secondary eruptions, condylomata, etc. is the standard procedure in Germany, and in most cases it is carried out by the examining specialist in his own consulting room. This is one of the techniques which the general practitioner seldom possesses, and the latter generally refers the patient to a specialist or, very occasionally, sends some serum enclosed in a capillary tube to a laboratory for dark-field examination.

Blood examinations for syphilis are carried out as a routine; those commonly used are the Wassermann reaction and the Meinicke or Klein or Kahn test. In some laboratories and hospitals the Chediak method is regarded with great favour as being rapid and giving fairly accurate results. All doubtful results from this method are checked by a subsequent Wassermann reaction.

*Treatment*—Cases of fresh syphilis with dark-field

examination positive and Wassermann test negative are treated by (1) one course of 12 intravenous injections of neosalvarsan (0.6 g. each injection) in the first 6 weeks (2) simultaneously with the neosalvarsan, one course of bismuth intramuscularly for a total of 12 injections, (3) a rest period of 6 weeks, (4) a repeat of the above courses of arsenic and bismuth alternating with rest periods of 6 weeks until the Wassermann reaction and spinal fluid are both negative. Three courses of arsenic and bismuth in 12 months usually suffices for a serological cure. Cases of fresh syphilis with both dark-field examination and Wassermann tests positive are given the same routine treatment but usually lasting 18 to 24 months.

Latent syphilis is treated by alternating courses of treatment and rest as for fresh syphilis for 24 months, or until serological and spinal fluid tests become negative.

Cases of paresis are given neosalvarsan by intravenous injection and bismuth by intramuscular injection, alternating with rest periods as for fresh syphilis—this treatment following upon the induction of malaria by the bite of an infected mosquito. Direct injection is preferred to the injection of infected blood because the reaction is more uniform.

*Tests of Cure*—At the conclusion of treatment Wassermann tests are made every 3 months during the first year, at the end of the first year the spinal fluid is tested. During the second year the blood test is done during the sixth and the twelfth month. A positive report at any time calls for resumption of treatments which generally means two or more courses of arsenic and bismuth. All tests being negative at the end of two years of observation following the cessation of 1 year's treatment, the case is considered definitely cured. Marriage is allowed for such 'cured' cases.

No penicillin had been used before the British occupation.

### Gonorrhoea

*Diagnosis*—Smears from urethra and cervix are taken and stained with methylene blue by Loeffler's method. This is a technique which British venereologists are taught to eschew in favour of Gram's staining method or one of its modifications. Having been in many of the German clinics and laboratories, however, and examined many stained specimens under the microscope *pari passu* with the German clinicians and pathologists, I am convinced that, provided the person carrying out the examination has had sufficient training and experience, the methylene blue method gives as good results in German hands as Gram's method in British hands. Moreover, in all doubtful cases the Germans are accustomed to use Gram's method as an alternative

In regard to cultures of material from urethra and cervix, the German practice appears to vary. In university skin and venereal disease departments cultures were routine, though under present conditions there is such a shortage of material for making the culture medium that few clinics are able to continue the routine. Apart from the university departments, the larger hospitals usually had cultures made as part of the routine examination, but the smaller hospitals, the general practitioners, and most of the private venereal disease specialists were not in the habit of examining by culture.

The Germans either know little or nothing about the employment of the gonococcal complement fixation test on samples of blood drawn from patients, or they do not think that the test yields any significant information.

*Treatment*—The general tendency in Germany for the past two or three years has been to use sulphathiazole (marketed under trade names such as eleudron, cibazol, etc.), but most German venereologists are somewhat hazy about the best methods of using the drug because they have had no opportunities for research and no access to publications from abroad. Those German venereologists whose standard of skill in the use of sulphathiazole is high give a routine course of treatment of 15 tablets on the first day, 12 on the second, 10 on the third, and 8 on the fourth, a total of 22.5 g. in 4 days. This is frequently followed at a week's interval by a similar course as an insurance, especially in women. British venereal disease specialists would be inclined to think that the total given is not great enough, and that the treatment should last 5 days instead of 4, but from the case records which have been studied the above method seems to give reasonably good results.

As is the case all over the world, successful results of sulpha treatment have tended to decrease owing to the development of sulpha-resistant strains of gonococci. The German venereologists state that about 40 % of their cases of gonorrhœa are sulpha-resistant, i.e. are not cured by one such course as above described. They are accustomed in such cases to induce fever in the patient by injection intravenously of foreign protein, or, in some cases, 1 or 2 c.cm. of a 40 % solution of oil of turpentine may be injected into the muscles of the buttock. This procedure is somewhat painful and produces temperatures in the region of 103–4° F. At the height of the fever, or immediately after, sulphathiazole is given in amounts of 15 tablets a day by mouth, and this is sometimes accompanied by the intravenous injection of 10 c.cm. of a 20 % solution of sulphathiazole. By means of these rather heroic measures they claim that, of the 40 % of sulpha-resistant cases, half are cured. This leaves 20 % of all cases

for which the methods of treatment current before the discovery of the sulpha group of drugs must be used.

Apart from sulphathiazole the Germans use protargol, silver nitrate, izal, mercurochrome, and similar antiseptics for local application. Before the British occupation the Germans had no experience of penicillin for the treatment of gonorrhœa.

*Tests of Cure*—Apart from a disinclination to use cultures, the German venereal disease specialists adopt much the same criteria as are accepted in the United Kingdom and the United States of America. Examination of the urethra by means of the urethroscope, massage of the prostate and microscopic examination of stained specimens of the expressed fluid, and, in many cases, provocative agents such as the intravenous injection of a gonococcal vaccine (the last a procedure of doubtful utility) make up the general test for cure in the male. German venereal disease specialists are very devoted to provocative methods as part of the test of cure and carry them to limits far beyond any that would be thought suitable in the United Kingdom. For example, within 4 to 6 days after completing treatment the male patient is submitted to massage over a straight sound and to dilatation with Kollmann's dilator. In addition, Lugol's solution, diluted 1 in 4, or 3% hydrogen peroxide are instilled into the urethra and retained for up to 5 minutes. Women are not submitted to mechanical provocatives, but concentrated Lugol's solution is injected into the cervix. In addition, in both sexes, intravenous injection of gonococcal vaccine is used as a provocative.

### Public Health and Legal Aspects

*Incidence*—Cases of venereal disease have never been notifiable, i.e. by names and addresses, nor, even, has reporting only in terms of numbers been the law in Germany. So the determination of the number of fresh cases of venereal disease occurring each year was largely a matter of guesswork. On occasion, by special Reich decree, a census of fresh venereal disease cases has been ordered to take place in a named month of the year, but this appears to have been done recently only in 1934 and 1940. From the figures so obtained a calculation of the venereal disease incidence for the particular year and for intervening years has been made. The results, however, can hardly be considered satisfactory, since the incidence in Germany was reported to be lower in the early years of the war than before the war, at a time when, in every other

country where records were available, there was found to be an increase

The standard law on venereal disease in Germany is the Law of 1927, in which there is no provision for a return by the doctors of the number of fresh cases of venereal disease seen by them.

**Case Finding**—There has been in Germany an obligation on doctors who see fresh cases of venereal disease to try to find the source of each infection and to get the person examined and, if necessary, placed under treatment. This obligation has apparently had no specific legal basis but has been a professional duty laid upon doctors by the *Arztekammer*, the Medical Association. This appears to be the situation so far as Reich legislation is concerned, but individual states or *Länder* have introduced their own laws, not only on this point but also on the reporting of fresh cases.

Investigation of the system of source finding or contact-tracing as actually practised in the British Zone brought to light two methods which, together with a third method, of doing nothing at all, appear to have been the custom. In the first method a doctor would diagnose that Mr A had venereal disease and would question him as to a possible infectious source, if he succeeded in eliciting a name and address, he would write to the woman and tell her she should either come to him for examination or, if she chose to go to another doctor, should send a certificate to the former doctor. If neither attendance nor certificate were forthcoming within a reasonable time, the first doctor would then send the woman's name and address to the Health Office of the area in which she resided. The medical officer of health would then write to the woman telling her of the circumstances and inviting her to present herself for examination either at a centre named by the medical officer of health or by a private venereal disease specialist. If no notice were taken of this, the name and address would be sent to the police and the woman would then be arrested (if found), flung into prison, compulsorily examined and, if necessary, treated, generally in hospital.

In the second method, the doctor first seeing a fresh case would get the name and address of the infectious source and transmit this

information direct to the Health Office, the procedure would then be the same as in the first method.

The third method, that of doing nothing at all, appears to have been much the most commonly used, except in the case of venereal disease specialists working at the universities and some of the more responsible privately practising specialists, these *venereologists* tried to carry out their professional obligations and their duty as citizens.

In the absence of records of the number of fresh cases of venereal disease seen by an individual doctor, it is, of course, impossible to assess the ratio of infectious sources reported by him to the number of cases seen, and therefore impossible to judge of the doctor's zeal in source-finding. It is not improbable that many sources were not even inquired for, or that, if they were discovered, the knowledge was suppressed for one reason or another.

Failure to maintain attendance for treatment and/or observation is an offence under the Venereal Disease Law of 1927, and the same law compels the doctor first to attempt to get the patient to return to him, and, if that fails to notify the Health Office, which then attempts by letter to secure the same end and calls in police action if that in turn fails. As it is part of the same law that a patient who knows he has venereal disease must be treated, there is an adequate legal basis for securing case-holding until the physician is satisfied that the patient is no longer liable to spread venereal disease. As in the case of source-finding, however, in the absence of records of numbers of fresh cases seen by doctors it is impossible to assess how many of these proceed regularly through treatment to cure, and what proportion of them default after more or less insufficient treatment.

**Health Visitors**—In most areas there are no health visitors and social service workers to deal with venereal disease problems, though they appear to exist for dealing with such matters as tuberculosis and maternity and child welfare. In some of the larger towns, for example Hamburg, Düsseldorf, Hanover, there are health visitors for venereal disease, but these are women (usually nurses) who sit in an office, maintain a card index of examinations of prostitutes, and assist the venereal disease specialist at such examinations.

They seldom or never undertake contact tracing by personal visit or try to win back defaulters to treatment

**Prostitution and Brothels**—The Venereal Disease Law of 1927 makes prostitution a criminal offence and prohibits brothels. In spite of its somewhat legalistic tendency, the German mind finds no incongruity between the provisions of this law and the existence of prostitutes and brothels in every large town in the British Zone. It was calculated recently that Hamburg had about 400 prostitutes in 43 brothels and Brunswick 95 prostitutes in about 16 houses. Kiel, Lubeck, Flensburg, Hanover, and the towns of the Ruhr and the Rhineland all present the same picture. The organization varies in detail, but on the whole follows the same general pattern, and for purposes of description the control and regulation of prostitution and brothels in Hamburg will be selected.

The control and regulation are conducted by a branch of the Police called the "morality police" (sixteen men in Hamburg). The personnel are recruited from the regular police force, and there is a rule that each man must be married and over 35 years of age before acceptance for the "morality police" branch. There is a period of three months' training at a central school in Berlin, where the curriculum contains lectures by lawyers, public health officials, etc. The course is entirely theoretical, and after passing an examination the trainees are returned to their original towns. They are then allocated to a district in company with a senior and experienced member of the force, and learn the job on the apprenticeship basis. In general they wear plain clothes, but hold warrant cards and are paid and administered as part of the normal police force. Their duties consist of patrolling the part of the district assigned to them (which is continually being changed), watching for instances of solicitation, and keeping an eye on women in cafés, bars, restaurants, etc., whose behaviour raises the suspicion of promiscuity, whether professional or amateur. In conjunction with the uniformed police, and, since the British occupation, with the military police, frequent raids on selected districts are made, during which 100 to 150 women of all sorts may be arrested, flung into gaol, and examined next morning at the

hospital reserved for such purpose. In addition to examination rooms and record offices, the hospital has wards containing about 180 beds. All the wards are, in effect, prisons, the inmates are locked in and some of the wards are watched by wardresses drawn from the police.

The venereal disease specialist in charge of this hospital, together with his assistants, carries out the examinations of the women brought there by the civil or military police, and those found to be suffering from venereal disease are hospitalized and treated and not released until the specialist certifies cure. Those not found suffering from venereal disease are required to report again at either weekly or fortnightly intervals for repeat examinations until such times as the specialist no longer requires them to do so.

If, during the period of treatment or examination, the police can get other evidence that the woman is a prostitute, she is then confronted with the alternative of living in a brothel or taking some work and giving up prostitution. The latter alternative is so hard for most girls on account of the triple stigma of prostitution, prison, and possible venereal disease, that it is not surprising that the majority go to swell the population of the brothels. In some cases private charitable organizations maintain homes (called *Doors of Heaven*) for the reception and rehabilitation of these women, but there seems to be little public recognition of the need to assume responsibility.

Once a woman has elected or been forced to become a prostitute she must live in a brothel and be medically examined twice weekly by the venereal disease specialist. She is provided with a book with particulars of her name, age, nationality, etc., and bearing a passport photograph. The book also contains pages on which the dates of examinations, results, and initials of the specialist are entered. The book must always be produced on demand by a member of the police.

By means of local police decrees, which are upheld by the local law courts, the employment of prostitutes in cafés, bars, restaurants, theatres, etc., is prohibited. Offending employers are fined for a first offence, and a second offence results in loss of licence to trade. In conformity with these local decrees,

employers in categories similar to the above are compelled to notify to the police the name and address of every female worker newly employed. The "morality police" then go through their card-index of prostitutes to ensure that the employee is not a prostitute.

The brothels are situated in certain streets, and are placed under the general administrative care of one man, who usually has a subordinate for each house. Most of the rooms are exceedingly small, and in them the prostitutes are expected to live, sleep, and work. The women appear to be well informed regarding their own protection from infection with venereal disease, and each prostitute has her own supply of condoms which, apparently in the majority of cases, she insists must be used by her clients. The brothel district is placed out of bounds to British troops, and periodic raids by the military police take place, during which the houses are searched from cellar to attic. It should be recorded that in Hamburg the military police and the civil authorities co-operate very closely, and thus has been the means of detecting and bringing under treatment many women and girls other than registered prostitutes whose way of living would inevitably involve the spread of venereal disease, not only amongst civilians but also amongst British troops.

In places other than Hamburg the routine examination of prostitutes and women suspected of spreading venereal disease is commonly carried out either in the Gesundheitsamt itself or in a building nearby. The examination is often performed by an assistant of the Amsarzt, who need not be necessarily a venereal disease specialist.

In general the routine weekly and twice-weekly medical examination of prostitutes cannot be too strongly condemned. The conditions under which the examinations are carried out militate against the successful search for venereal disease, as the women have ample opportunity for frustrating the purpose of the inspection by previous vaginal douching. It is obviously a strong temptation to any woman who earns her living by prostitution, and who knows that discovery of venereal disease will put her out of business for anything up to three months, to try to arrange that venereal disease shall not easily be found. In result, the so-called examination of prosti-

tutes by doctors is merely prostitution of examination by doctors.

Whatever the attitude of society to prostitution, it is perfectly clear that to the epidemiologist a prostitute without venereal disease is of as little consequence as anybody else without venereal disease, and that a prostitute with venereal disease is of exactly the same concern as any other woman who has venereal disease. All who have it can spread it, therefore the programme is to find them, whoever they are.

### The Venereal Disease Problem after the Surrender of Germany

For some two or three years before the unconditional surrender of Germany the principal towns and cities had been constantly subjected to heavier and heavier bombing, with the result that by the time the British forces took over the British Zone of occupation there was widespread destruction of towns, including residential and industrial districts, and almost complete arrest of transport, while communications were maintained almost solely in the most primitive ways since postal services, telephones, and motor transport had all broken down. Unless a doctor had a bicycle his only means of visiting his patients was on foot, and the same applied to patients visiting their doctors. Even the ambulance service had suffered severely, mostly through shortage of fuel, and it was common to see desperately ill patients being conveyed to hospital on hand-carts. The hospitals themselves had often suffered severe damage, either directly to their structure or indirectly to their functions because of interruption of water, gas, and electricity supplies. The virtual stoppage of road and rail transport caused interference with the distribution of all types of medical supplies, with the result that there were often acute shortages of drugs, dressings, anaesthetics, etc. At this time most wounds were bandaged with paper which, in more fortunate times, would have been used only as toilet paper.

As can readily be understood, strenuous efforts were made by the British public health officers to restore the hospitals to something approaching efficiency, and their efforts were supported by those responsible for production and distribution of medical supplies. To tide over the worst period, stocks of drugs, etc. were obtained from captured Wehrmacht stores.



Since the treatment of venereal disease was not concentrated in public clinics attached to hospitals, but, as we have seen, remained predominantly in the hands of private doctors, it is easy to understand that venereal disease specialists, lacking the organization of the hospitals and the priority of attention from British Military Government, were even more hard put to it to maintain a reasonable standard of skill and treatment. An endeavour was therefore made to direct as many patients as possible for treatment to the venereal disease departments of the university and municipal hospitals. In spite of all that could be done, local shortages of sulphathiazole occurred (Fortunately there was never any shortage of drugs for the treatment of syphilis). In some cases the German doctors' reaction to restricted supply of sulphathiazole for gonorrhoea was to give each patient some, so that in fact no patient got the optimum dose. This practice had to be forbidden, as otherwise there would probably have been a great increase in sulpha-resistant gonorrhoea.

The standard laid down was 5 g a day for 5 days. As was noted above, many of the German doctors were still adhering to a routine of 5 g a day for 2 days, and some opposition was encountered to the instruction to make it 5 g a day for 5 days. It transpired that I G Farben Industrie had had in circulation a leaflet on the uses of sulphathiazole in which the 2-day treatment was recommended. So great was the slavish adherence of many German doctors to this leaflet that its publication was forbidden until it was amended to the optimum dose mentioned above.

In the early days after the occupation of Germany there was so much emergency work that, necessarily, most energy was directed to short-term or *ad hoc* measures. It was always in mind, however, that sooner or later long-term measures would have to be introduced, and as a first step an instruction was sent out in October, 1945, to all German doctors, requiring them (a) to report each week the total number of fresh cases of venereal disease seen by them. It was specifically stated that names and addresses would not be reported. In addition (b) all medical officers of health were instructed to inaugurate and maintain a system of contact tracing, and to keep records of the number of sources reported to them and the number of these brought under treatment. All doctors were instructed to obtain from each new patient with venereal disease as much information as possible about the source of infection, and to

transmit the details without delay to the medical officer of health. All medical practitioners were instructed (c) to notify the names and addresses of venereal-disease defaulters to the medical officer of health, who was made responsible for using the powers given him by German law to bring the defaulters back to treatment. Finally, weekly reports in the case of (a) and monthly reports in respect of (b) and (c) were required to be sent to Military Government public health officers.

These instructions were sent out through the presidents of the various provinces in the British Zone, who represented the highest available constitutional authority, and they were made responsible for the implementation of regulations which affirmed the provisions of existing German law, except in regard to (a), reporting of fresh cases, which, as noted above, had in many States of Germany been the custom before the British occupation.

German venereologists are unanimous that venereal disease increased enormously in Germany during the war, and more particularly since the middle of 1944, but they are unable to do more than speak of impressions. They believe that syphilis is very much more increased than gonorrhoea, an opinion which is confirmed by the carefully kept statistics of Denmark and the other Scandinavian countries. In these countries it has been found that the incidence of syphilis has increased to eight or ten times what it was in 1940. In all probability, having regard to the much greater social and economic disorganization in Germany, especially during 1945, together with the very large movements of population, and, more recently, of German refugees from parts of Germany outside the British Zone, it would not be unwise to say that the number of fresh cases of syphilis is about twenty times that in 1939-40. It is also prudent to forecast that, at least until 1948, the incidence of syphilis will tend to go on increasing, not only in Germany but all over Europe. It happened after the last war when, on the whole, there was very much less disorganization of the social and economic framework and much smaller movements of population than now.

From the end of October, 1945, it became possible to assess the incidence of gonorrhoea and syphilis, not only in total for the Zone, but especially in the population centres such as Hamburg, the Ruhr, and the British Sector of Berlin.

The number of cases of venereal disease in the

British Zone in 4-weekly periods from November, 1945, to September 1946, was

1945	<i>Syphilis</i>	<i>Gonorrhœa</i>
November	2,352	6,648
December	2,465	6,196
1946		
Dec. 30 to Feb. 2	3,704	9,382
Feb. 3 to March 2	3,335	7,571
March 3 to March 30	3,097	7,057
March 31 to April 27	2,844	6,915
April 28 to June 1	3,963	9,788
June 2 to June 29	3,184	8,724
June 30 to July 27	3,726	9,006
July 28 to Aug. 24	3,949	8,786
Sept. 1 to Sept. 28	4,090	8,553

A German Public Health Advisory Committee was formed, consisting of one German public health officer from each of the four provinces of the Zone and one from Hamburg, which counted as a province. The five doctors met each month at the headquarters of the Health Branch of Control Commission, and to them was entrusted the detailed working out of public health policy in the British Zone. It must be clearly understood that the Committee was purely advisory and had no executive functions whatever, but it proved of enormous value.

#### Venereal Disease in Displaced Persons—

The care of displaced persons was primarily the responsibility of U N R R A., who were helped materially by the Army Medical Services and British Military Government. As there was considerable uneasiness concerning the possibility of venereal disease in displaced persons, a tour of displaced persons' camps was accordingly undertaken with the specific object of investigating the venereal disease situation amongst displaced persons, and sufficient camps were visited to account for 60,000 displaced persons, i.e. 10 per cent. of the then displaced persons in that area. All the doctors in these camps were interrogated and their case records inspected, and discussions took place with interested R A M C officers, who had considerable responsibilities for the medical supervision of displaced persons' camps. It transpired that, though conditions were ideally suitable for the spread of venereal disease, the numbers of fresh cases of gonorrhœa and syphilis were very small, both absolutely and in relation to the populations involved.

**Penicillin**—At an early stage it was foreseen that penicillin would prove of great value in Germany on account of its rapid action in the treatment of gonorrhœa, and preliminary steps were taken to obtain supplies which would become available when the German venereal disease organization had reached a stage at which it would be capable of dealing with the implications of what, to them, was an entirely novel method of treatment.

**Advisory Committee**—Before the time arrived for the distribution of penicillin a very important step had been taken in the public health organization of the British Zone.

Soon after its formation the Committee was informed that it was proposed to make certain alterations in the then existing venereal disease organization. They were told that treatment would be available free without any question of ability to pay, or discussion between private insurance companies and public assistance bodies as to their respective liabilities. They were further informed that, in order to increase the control by the medical officer of health over the venereal disease activities of the private doctor, the latter in each case would have to maintain a confidential register of all patients seen by him suffering with venereal disease. Further it would be the duty of public health authorities to appoint, on a whole-time basis, venereal disease specialists to exercise an overall supervision of all aspects of the venereal disease problem in their area, including a detailed supervision of the treatment of individual cases by the practitioners. These in turn were to be required to submit at suitable intervals copies of their case reports showing progress and treatment. In addition the Advisory Committee was asked to obtain from the universities schedules of their treatment for the venereal diseases, and, with the aid of the professors of venerology, to draw up a standard routine for application to the whole Zone. This fairly considerable task was duly carried out by them and the results of their work were issued as an instruction to all doctors in the British Zone.

It will readily be seen that one object of the above scheme was to facilitate the setting up of clinics for the treatment of venereal disease, and when, early in 1946, it became apparent that supplies of penicillin would be available, further impetus was given to this

tendency. It must be understood that penicillin had at this time a very high black-market value, and therefore any plans for the use of penicillin in the treatment of gonorrhœa had to be considered very carefully, to avoid, as far as possible, leakages into the black market. It was felt that the most prudent course was to select the university venereal disease departments as the only centres where penicillin would be available. As the need became too great for these centres to cope with the problem, further centres in the municipal hospitals of the large towns were set up, but penicillin was never available for private practice.

Most of the selection of centres of specialists was done by the Advisory Committee. As none of the German venereal disease specialists had had any experience with penicillin, arrangements were made through the courtesy

of Sir Edward Phillips, KBE, DMS of the Rhine Army, for the selected German specialists to see demonstrations at the Army Venereal Disease Treatment Centres. Detailed instructions were then sent to the chief public health officers of all the provinces and Hamburg, giving not only details of dosage, care of penicillin, etc., but specimen record sheets for the use of the hospital dispensaries and clinics.

The final results of the efforts described above to deal with the venereal disease situation in the British occupied Zone of Germany may not be seen for some time to come.

I wish to express my indebtedness to the Controller-General of Health Branch, British Element of Control Commission, for permission to publish this paper, and for kindly supplying the figures for the table.

## DISCUSSION ON THE PRECEDING PAPER

DR G L M McELLIGOTT (the President) said that, inaccurate though the information given by the methylene blue method might be, he nevertheless thought a single blue stain was probably more informative than a bad Gram stain.

He still felt that at the end of two days one usually knew whether sulphonamides were going to be effective or not. In his own experience of the use of the sulphonamides, when they were at the height of their popularity and the height of their efficiency, and the two went together, a course lasting two or at most three days, gave as good a result as one of fourteen days. He personally had not had much experience of the intravenous sulphonamide treatment of gonorrhœa, but he had had the opportunity, during the war, of using it in a good many cases of meningococcal meningitis in which the immediate response to treatment was far better than that when the drug had been taken by the oral route.

He thought they would all agree that in venereal disease cases treatment must be absolutely free. The American authorities had undoubtedly recognized that, and had said that one of the reasons why the incidence of syphilis was brought down to such a low level in this country and in the Scandinavian countries before the war was that the treatment provided was free. Even now he believed a patient in America had to pay a small fee at each clinic attendance. This must lead to premature default.

LT-COL WILLCOX asked how rigorously and how conscientiously the medical examination of prostitutes was carried out, and whether Dr Curtis had any idea how many contacts the average prostitute had without contracting some disease.

He said he understood that penicillin was in general use for treating gonorrhœa, but not for syphilis. He would like to know what the schedule of treatment had been for syphilis when Dr Curtis was in Germany. They had been told what it was before the war, but he did not understand what it was at the present time, or whether it was uniform throughout the zone. He would also like to know whether there was any equivalent of the V 15 traveller's booklet for patients moving from zone to zone, and whether the Russians were co-operating with this system of treatment.

DR MARSHALL said that continental public health services for venereal disease had always differed from our own. With regard to displaced persons, the French in 1945 did make some attempt to find out what had happened to the men who had been taken into Germany for forced labour and they tried, without much success, to do serum tests on the men coming back from Germany. Those coming through Paris were subjected to medical examination, and blood samples were taken. Naturally there were a large number of people in transit who made their own way home, but it was possible to do many thousands of blood tests. The method in the first instance was a simple and quick slide test of the Kline variety, and a photographic picture of the result of the test was made, which was eventually appended to the man's papers. If a positive result was obtained the authorities intended to look out for the man and have further tests. The number of positive results they found was relatively small—one or two per thousand. The system unfortunately failed because the men, after leaving the distribution centres, scattered all over

France and there was no adequate method of contacting them. As a result, out of the thousands of people in whom they found positive tests only a few hundreds were eventually traced, subjected to re-examination and brought to treatment. Dr Marshall asked whether Dr Curtis had obtained any information about antibiotics, which according to certain American publications the Germans were said to have found, and which were stated to be almost as effective as penicillin in certain conditions.

DR W N MASCALL remarked on the fact that German venereologists were trained for four years against perhaps 130 hours tuition in this country. He thought four years a very good space of time for the training of a specialist. He also thought that if what Col Willcox had said was true, that penicillin was not in general use for syphilis, at least the Germans knew where they stood which was more than was the case in this country at present.

Dr Mascall said that for some time before he left the Whitechapel Clinic they were experiencing considerable difficulty with the Kahn test, and they came to the point where a positive Kahn after treatment was practically ignored. For a period they relied upon the Wassermann Reaction alone. All the tests were a bit unreliable at that time but the Kahn more so than the others. The origin of the trouble was finally traced to some deficiency in the diet of the guinea-pigs. With regard to intravenous sulphur drugs, some years ago they tried at the Whitechapel Clinic the drug sulphamezathine, and the results were if anything better than those they got from the oral administration of the same preparation.

DR OSMOND asked Dr Curtis what sort of Wassermann test was used in Germany. With regard to the Kahn test, there was no question but that very bad samples of antigen were made during the war. Most of them were produced in England and they were not up to the same standard as those produced by Kahn in his own laboratories. He had gone into the question of the Kahn antigen made for the Army and it seemed to him that the controls which were used were not adequate for the accurate turning out of an antigen which was sufficiently sensitive and sufficiently specific.

Dr Curtis had stated that displaced persons spent most of their time fornicating and yet there was little or no venereal disease. Could Dr Curtis give the reason? He also wondered if they could be told a little more about the amount of venereal disease in Germany. He thought he was safe in saying that the amount amongst the occupying forces was now very great, and consequently there must be a very high rate amongst the German population. Was there a high rate at the time Germany was occupied? Also, could Dr Curtis tell them a little more about contact tracing. Had there been any appreciable success in finding out the contacts and getting them treated?

DR C S NICOL said he had heard that homosexuality had been a great problem under the Nazi régime in Germany, and he wondered whether Dr Curtis came across that during his stay there. With regard to the methylene blue stain, he would have thought that although this method might with practice have been sufficient in male cases where there was usually only one organism present in female cases where there were mixed organisms one could not differentiate between those which were gram positive and those which were gram-negative.

He was interested to hear Dr Curtis's account of prostitution in Germany and of brothels there. At the beginning of the war, when in the B E F he had had the chance to inspect the brothels in France and his impression was that they were similar to those in Germany—the same system of compulsory examination of having a form with a photograph on it really the equivalent of a passport on which the tests were recorded, and also the same complete lack of success of this method of checking venereal disease.

DR FLYNN said he had seen a great deal of venereal disease amongst German soldiers during the last year of the war and he had noticed that the disease in them was in a far more advanced state than it was amongst British troops. The German medical officers seemed to have little knowledge of the subject. On enquiry he was told by German medical officers that their medical students went from place to place in the army and obtained their training at any hospital which was near at hand. If a medical student was a good Nazi he was bound to qualify. The Germans themselves were very amenable to any suggestions, but they seemed to have very little medical equipment left at the last stage of the war and they were doing the best they could with very little material.

DR CURTIS in reply said that the German prostitutes had to report for medical examination once or sometimes twice a week, in their own time and in their own state of preparedness or unpreparedness as they chose. He had watched a number of those examinations taking place, particularly in Hamburg and Brunswick, and he was quite satisfied that the examinations were carried out conscientiously but the number of prostitutes found to be infected with venereal disease was relatively small. He attributed this fact to the custom of their douching themselves thoroughly before going for examination. They were well aware that if they were found to have venereal disease they would be put out of business for three months. The efficacy of any medical examination carried out under such conditions was doubtful. His personal opinion was that unless it was possible to keep the woman for 48 or 72 hours before the examination under such observation that she could not douche, it was quite useless to examine her and particularly useless and dangerous to append a specialist's initials to the results of such an examination.

Dr Curtis said it was seven or eight months after their first application for penicillin before it arrived. He thought it was fair to say that the Ministry of Health, and particularly Col Harrison, had played a large part in expediting the arrival of penicillin. They had never considered asking for penicillin for the treatment of syphilis, because they took the view that penicillin was in no way superior to arsenicals in sterilizing syphilitic lesions. As they were chiefly concerned with the short-term problem of infectiousness they did not feel justified in applying for this very expensive drug when arsenicals would do the job equally well.

As regards the V 15, there was a similar system of transfer card available throughout Germany which was operating during the time he was there but only in a very restricted manner because the amount of movement permitted to German civilians was very small for reasons entirely unconnected with venereal disease. Lack of transport and the difficulty in getting permits for movement were chiefly responsible.

He was very interested to hear that the French had tried to perform serum tests for syphilis on all the millions of French people who had moved back from Germany into France, at a tremendous rate, from May, 1945. One of the other ideas mooted was that of mass radiography in order to find those who had contracted tuberculosis, but that was regarded as being impracticable. In the early days the stream back to France of displaced French people could be adequately controlled only at such places as the crossings of the rivers, and once they got over the rivers they just went their own ways, it was surprising that the authorities had managed to get as many serum tests done as Dr Marshall had mentioned.

Dr Curtis never came across any evidence in Germany of antibiotics being produced, with the exception that occasionally a pathologist or bacteriologist had managed to manufacture small quantities of penicillin by the "jam-jar method" on a laboratory bench. He could not say what kind of Wassermann test was being used, but after seeing the WR performed he accepted the German's statement that they were adhering to one of the standard procedures as laid down by the International Conference before the war. With regard to Dr Osmond's question as to why displaced persons had so little venereal infection, the chief reason was that most of the persons in displaced persons' camps at the time he visited them were Russians, Poles, and a few Eastern Europeans, mostly Slavs. Their methods of dealing with such anti-social conduct as one inmate of the camp passing venereal disease to another were sufficiently drastic to prevent much spread.

Dr Curtis said that syphilis in Germany during

the first six months of this year was five times the rate in England and Wales during the whole of 1944, and gonorrhoea between eight and ten times. How those figures compared with the figures in Germany before the occupation he did not think anybody could say, because Germany had never had any regularly compiled statistics of the incidence of venereal disease.

There was no legal obligation on German doctors to trace contacts. There was a professional duty laid upon them through their medical association by the Minister of the Interior to find out sufficient particulars of contacts to enable them to be traced. In order to improve the situation each doctor was asked to report the number of fresh cases he had received and the number of contacts he had traced, or, at least, to report the results of his efforts to trace the contacts. That was one of the subjects of considerable discussion when, in Berlin, the British, Russians, French, and Americans were trying to devise a new venereal disease law, based on the law of 1927, which should apply throughout Germany. It was thought that if the provisions of the law bore too harshly on the members of the public in the opinion of the doctors, then the doctors could sabotage it by refusing to diagnose a venereal disease. How far could they go before arousing the antagonism of the doctors to the measure on the grounds of the patients' interest? It was not a very easy subject on which to reach a conclusion.

Homosexuality was supposed to be frequent in Germany before the war, and particularly in Berlin. There still existed in Berlin a well-known club called "The Femina," which, before the war, was reputed to be the resort of a large number of homosexuals of both sexes. During the occupation of Berlin by Allied troops homosexuality had not been much in evidence. He had not been much interested in the spread of venereal disease by homosexuality because women greatly outnumbered men in Germany, partly on account of the death rate in the services, and also because some millions of prisoners had not yet returned.

He had been struck by the low standard of venereological knowledge displayed by the German Army doctors, and he had never seen venereal disease treated under worse conditions and with more ignorance. He had since thought that the Germans had got a very serious problem in front of them sooner or later when the ex-members of the Wehrmacht began to develop, as they would do, the sequelæ of the inefficient treatment of syphilis. They had tried to warn the German people of that danger by having posters put out advising all ex-members of the Wehrmacht who had had venereal disease to get themselves re-examined at the local clinics.

## A DISCUSSION ON PENICILLIN THERAPY IN VENEREAL DISEASES IN WOMEN\*

Dr G L M McElligott (the President) said that Dr Eva Gallagher was to have opened the discussion but that she unfortunately could not be present. He felt that this subject was so important that the discussion on it should still take place, and he hoped members would give their experiences not only of the treatment of gonorrhœa but also of syphilis

### DR MARY MICHAEL SHAW

Dr Mary Michael Shaw said that up to date she had treated with penicillin about 100 women suffering from syphilis. The cases were not selected, some were not acute but had been given penicillin with the object of getting specimens of blood in order to ascertain the blood level of penicillin. Her results were not of any great value because she had not given penicillin by itself every patient had also had arsenic or bismuth unless there was some contra-indication. Only one or two patients had had penicillin and nothing else, and in those the results were dramatic. An adult congenital syphilitic improved greatly and in an old lady aged 70 a gummatous ulcer on the leg healed very quickly. She had seen 2 cases of severe urticaria, in 6 other cases out of the 100 there had been a local urticarial rash.

Dr Shaw thought there was so little advantage to be gained from penicillin for gonorrhœa in women that she did not give it unless there was a complication. Nobody had been bold enough to reduce the stringency of the tests of cure. If women patients were to be kept under observation for 3 months only 4 days would be saved by giving penicillin as opposed to a sulphonamide—at least the patients might become non-infective 4 days earlier—but as a rule any spread of infection took place before patients attended the clinic. Very few women went out of the clinic and knowingly infected other people.

Penicillin had been given to about 60 cases of gonorrhœa in women in whom a complication such as arthritis or some pelvic inflammation was present. There had been no ill-effects and the results had been surprisingly good. She had not had the experience of treating a frankly congenital syphilitic child with penicillin. Most of the babies had been born in the hospital, and the mothers had had full treatment during pregnancy with penicillin plus arsenic or bismuth.

### DR. JEAN MORTON

Dr Jean Morton said that in the Royal Air Force Medical Service 8 cases of secondary syphilis in women had been treated with 2,400 000 units of penicillin. 5 were followed up for 1 year, and 3 for 18 months. There were no failures

amongst the 8 cases. A second group of 8 cases, 6 with secondary syphilis and 2 with early latent syphilis, was given 2 400 000 units of penicillin combined with N.A.B., 0.3 g given twice weekly plus bismuthyl 0.2 g, given once weekly for a period of 6 weeks. Three patients had been under observation for 6 months, 3 for 9 months and 2 for 12 months. There were no failures in this group. A third group of 7 cases all with secondary syphilis, had been given 4 000 000 units of penicillin plus a total of 3.6 g of N.A.B. and 1.2 g of bismuthyl. All 7 cases were followed up for 6 months with success.

Her impression about giving penicillin alone was that the reactions were as frequent as when arsenic was given alone. There was no case of dermatitis but there was 1 case of œdema with urticaria. When extensive lesions were accompanied with toxicity the improvement in the patients' conditions was more rapid when they were given penicillin alone than when they were given arsenic alone. When complications of gonorrhœa were present, such as arthritis or salpingitis she thought that improvement in the clinical condition was more rapid with penicillin than with sulphathiazole. A woman with marked arthritis of the elbow joint was given 300,000 units of penicillin. 10 injections of 30 000 units 3-hourly for 30 hours. The day after completion of treatment she could move her arm, and on the third day after completion she was able to do her hair.

Dr Morton said she did not give penicillin in cases of gonorrhœa until the report of the serological test for syphilis had been received. In the meantime she carried on with sulphathiazole.

### DR. ROBERT LEES

Dr Robert Lees said he had read in a medical journal that penicillin was liable to cause abortion in pregnant women. He had never seen such a case though he had now treated many pregnant women.

He had observed some cases of interest. One was a boy of 18 months who was referred to the dermatologist with an extensive eruption around the mouth. At first this was thought to be a congenital syphilitic lesion but it was proved that the remainder of the family were normal and the mother attributed the infection to a nursemaid. The child made a rapid and satisfactory recovery with penicillin. Another child had extremely gross congenital syphilis such as he had never before seen. All the classical signs were present with a bullous eruption on the palms and soles, snuffles and laryngitis and a café-au lait colour. The

This discussion took place at the meeting of the Medical Society for the Study of Venereal Diseases on June 29 1946

child was very much under weight and had a large liver and spleen, but, after treatment with penicillin by injection, had prospered and was gaining weight rapidly. The bullæ had disappeared, and the child was doing better than he would have expected under any other system of treatment.

In a third case the mother had been treated, during pregnancy, with penicillin, 2.4 mega units, she was confined somewhat prematurely, and the baby weighed 1½ to 2 lb. It was a puny child and made little or no progress during the first 4 weeks of its life. There was so much doubt whether it would survive that it was decided not to give penicillin by injection, but penicillin was added to its feeds. From that moment the child began to gain weight and thrive. Unfortunately the nurses were unable to collect the baby's urine, so it was not known how much was excreted. Treatment was continued for 14 days. The dosage was double the amount usually given by injection, and 2,000 units was given 3-hourly. The child was under observation and was still thriving and gaining weight. It had not been given any other treatment. It had a negative blood test at birth.

The speaker wished that an obstetrician would give a dose of penicillin in cases in which a Caesarean section was about to be performed so that after operation the concentration of penicillin in the maternal and foetal blood could be compared. He had read various American reports which were not very conclusive but which did indicate that penicillin got into the foetal circulation. He had been watching for a case of ophthalmia neonatorum in a child of a woman treated for gonorrhœa with penicillin, but up to the present had not seen such a case.

#### DR BETTY WALKER

Dr Betty Walker agreed with what Dr Morton had said regarding gonorrhœa. Over 100 cases had been treated since Jan. 1, and there had been 6 relapses. She was sure that infection in women cleared up more quickly with penicillin than with the sulphonamides, and that the complications recovered more quickly too.

With regard to syphilis, about 300 unselected cases had been treated—of latent, pregnant, early, and neuro-syphilis—and there had not been one severe reaction in any of them. The early cases had shown the same percentage of Herxheimer reactions as with arsenic. All these women found their general well-being much increased but she did not know whether this was the psychological effect of knowing that they had had penicillin, or the effect of the drug itself. About 30 cases of syphilis had been treated during pregnancy, all had had arsenic or bismuth also, so that she could not say what the results of penicillin alone really were, in any case it was too early. Thirteen infants had been born of women who had had penicillin and one course of arsenic or bismuth, all the infants had been negative to the Wassermann test and had remained negative. None of them had yet reached the age of 6 months, so that it was still too early to form a conclusion. A midwife in a hostel for delinquent women with

venereal disease had assured her that in an experience of 20 years the children born of the women who had had penicillin were much stronger than those who had been treated with arsenic alone. The infant which Dr Lees had mentioned weighed 2½ lb at birth, it was now 8 weeks old and weighed 6½ lb, an increase which seemed miraculous.

#### DR MARINKOVITCH

Dr Marinkovitch said that since the title of the discussion was announced in September, 1945, he had taken special interest in this subject and had treated 40 pregnant patients with penicillin. All the cases were in the primary or secondary stage of syphilis, and all were also given arsenic and bismuth. It was difficult to talk about final results but he certainly had not seen a baby with a positive Wassermann reaction and clinical symptoms born to any one of the 40 patients who had been treated. He thought that all mothers in the primary stage of syphilis should be treated with penicillin as pregnant women in the secondary stage took a longer time to achieve negative serological tests. He had observed the tonic effect of penicillin in female as well as male patients. He had been impressed by the effect of the combined arsenic and penicillin treatment in pregnant women, and had not seen an abortion due to this treatment. He had treated three infants with penicillin alone, with the most excellent clinical results.

With regard to gonorrhœa in women, the clinical results were not so dramatic as they had been in the early days of sulphonamide therapy. On microscopical examination of the urethral and cervical pus in such patients, numerous pus cells were seen but no gonococci. With regard to the treatment of gonococcal complications, his impression was that the results of penicillin therapy were not achieved rapidly. He had treated a man with synovitis of the knee and iritis with penicillin but with poor results, and finally had to give him a T A B vaccine intravenously to achieve cure.

#### DR JAMES MARSHALL

Dr James Marshall did not recall that any contributor to the discussion had mentioned treatment of syphilis with penicillin alone. Just a year ago Major Laird and he disclosed that they were using a combined treatment, and they were frowned upon and told that their technique was bad and that if they had given their penicillin properly they would have cured syphilis. He wondered what had brought the change of heart.

As far as the treatment of syphilis was concerned, in his clinic he now gave for primary syphilis 2,400,000 units of penicillin in aqueous solution, or 3,000,000 units in oil-wax suspension, combined with which he gave a 10-week course of arsenic and bismuth, either as neoarsphenamine once weekly, or arsenoxide twice weekly. For sero-positive and secondary syphilis, after one or two failures with the above treatment he had given the same amount of penicillin plus two courses of arsenic and bismuth, a total of 24 weeks' treatment.

He could not give any results, because this method had only been used for about 6 months.

He had treated about half a dozen women during pregnancy with penicillin and arsenic, and 4 had had their babies. The blood tests at 6 weeks after birth in the children had been negative in all cases and they had shown no clinical signs of syphilis.

Penicillin was a great advance on the sulphonamides in the treatment of gonorrhœa—first in the percentage of cases which were cured by one course of treatment, and secondly in the fact that the treatment could be completed in every case as there was no trouble from intolerance of the drug. It surprised him to hear Dr. Mary Michael Shaw say that she did not use penicillin in her cases.

#### DR. HEYWOOD

Dr. Heywood apologized for having no statistical figures to support the clinical impressions of his own experience at Newcastle. For the treatment of gonorrhœa, both males and females, a variety of methods with penicillin had been tried. All gonorrhœa cases were treated with penicillin immediately on diagnosis. He began by using 100,000 units in an aqueous solution spread out over 15 hours which required the keeping of the patient in hospital for that period of time. With that treatment, in the first series of nearly 100 cases, there had been no failures. In order to reduce the period during which the patients were kept at the hospital or clinic, the total dose was increased to 150,000 units spread over 8 hours. With that schedule there was a very high proportion of successes, and, of 3 cases that had failed 2 responded to a second course. The third patient responded neither to a second, third, nor fourth course of penicillin, nor to sulphonamide, and eventually had to have fever treatment.

Using penicillin in an oil wax suspension according to the recommendations of the Ministry of Health 200,000 units were given but this had temporarily been increased to 250,000 for ease of administration. In women there had not been any relapses except in one case in which it was difficult to distinguish between a relapse and a reinfection. In general the patients' histories were unreliable, and even if they admitted re-exposure to infection there was no evidence that they were reinfected. His impression was that females were cured by the first dose of penicillin, an impression borne out by biological tests, but this was so much at variance with his experience with male patients that he thought there was possibly something wrong with the follow up methods in the female cases.

He wished to raise the question of diagnosis in suspected gonorrhœa. This was a problem which arose under Regulation 33 B. A woman was named as a possible source of infection, and she was either persuaded or compelled to attend a special practitioner or a clinic. It then became the medical officer's task to decide whether she had gonorrhœa. It was a real problem to decide what tests and how many to employ before

discharging her as free from infection. Formerly, at Newcastle a blood test and three consecutive smears were taken, and if these were negative the patient was discharged but since they began to get contacts under 33 B so many female patients had been seen in whom gonococci could not be detected in the first, second or even in a sixth smear, that it seemed there must be a longer time for investigation and a more detailed follow-up. He had heard of contacts under 33 B being discharged on the strength of one smear, which seemed highly unsatisfactory.

Salpingitis in women had been miraculously cured by penicillin, but Bartholinitis seemed to be less rapidly cured with penicillin than with the sulphonamides. The results in gonococcal vulvovaginitis were disappointing.

Dr. Heywood had had only four beds available to women with syphilis for 1,000,000 inhabitants—a number entirely inadequate for the treatment of patients with penicillin by 3 hourly injections. The situation had, however, been helped by the issue of the oil wax suspension of penicillin. He was using penicillin with arsenic and bismuth. In such cases there had not been any serological or clinical relapses, and some of the patients had been under observation for over 12 months. A small number of early congenital syphilitic children had been treated, but the response was not as dramatic as had been hoped. His impression was that such patients treated with arsenic and bismuth healed more rapidly than the cases treated with penicillin.

#### DR. W. NEVILLE MASCALL

Dr. W. Neville Mascal said that he had investigated a small consecutive and unselected series of female patients most of whom had been admitted to hospital for treatment. As far as penicillin treatment of gonorrhœa was concerned he had been disappointed. Out of 42 cases 57 per cent. proved unsatisfactory in that gonococci had been present after a lapse of 7 days from the cessation of treatment. These cases had been tested in routine manner, namely smears were taken from the urethra and cervix, cultures from the urethra, cervix and vagina. He had not included the cases which merely showed a persistent gonococcal fixation test; the gonococci were actually either seen in smears or grown on cultures.

What did greatly surprise him was that in the series there were 12 patients treated for syphilis who had received 2,400,000 units of penicillin in hospital, and out of those 12, if he remembered rightly 5 still had gonococci present at the end of the treatment, either in smears or cultures. One remarkable case was that of a girl with gonorrhœa who received 200,000 units of penicillin in ethyl oleate, and 7 days afterwards she developed a Bartholinitis from which the gonococci were cultivated.

Clinically the cases frequently showed little improvement after penicillin. When dealing with the vagina one was not generally dealing with a straightforward gonococcal infection. There were trichomonas and other organisms which penicillin would not touch, and it was no good saying



"You are cured" as long as there was a discharge present, because the patients were not convinced. This appeared to be one of Dr Marinkovitch's problems. Patients had penicillin, and afterwards they might be cured of gonorrhœa, but they still had their symptoms and unless one did local treatment at the same time it was, from the patient's point of view, a waste of time to give them penicillin. He remembered when the sulphonamides came into use saying that they did not cure the discharges, and he said the same about penicillin.

In cases of vulvovaginitis he also obtained extraordinarily bad results. In this series there were only 3 children, but they all failed to respond to one course of penicillin. In fact one child had, altogether, 4 courses of penicillin, starting off with 150,000 units in water, she received 300,000 units in water but was still positive, she then received 300,000 units of penicillin in oil on two occasions and was still positive, finally the infection was cured by sulphadiazine. It might be suggested that she was being reinfected, but all the other members of the family had been examined and not one was positive, so that reinfection could be completely excluded. The other 2 cases failed to respond to a standard course of penicillin given in divided doses, which he thought the best method of administration.

He had been disappointed in the treatment of gonorrhœa with a single injection of penicillin in oil. He was sure that if the penicillin were spread over a longer period of time better results would be obtained. He was interested to hear from Dr Curtus, who had recently returned from Germany, that the same difficulty was being experienced with vulvovaginitis and they had come to the conclusion that some other treatment besides penicillin was necessary. It was suggested that they should go back to œstrogen therapy as an adjuvant to penicillin.

Dr Mascall said that his patients had been remarkably free of complications. He had seen a number of Herxheimer reactions in the treatment of syphilis but not more than one would expect. The question of swollen buttocks was a problem. He had treated a ballet dancer whose buttocks swelled to five times the normal size but finally settled down satisfactorily.

Since reporting 2 cases of early abortion during the treatment of patients with penicillin, he had read a lot about the action of penicillin on the uterus and had come to the conclusion that it was more marked in the non-pregnant than the pregnant uterus. The reaction was probably due not to the penicillin *per se*, but to certain impurities in the final product. At one time when giving penicillin in water he had thought that if the quantity of fluid in the injection was reduced there would be less pain, and he tried to reduce the amount to 2 c cm for 200,000 units, but was alarmed at the number of collapses which his cases experienced. He reported this to the Ministry of Health, and they furnished him with some pure sodium penicillin, and on his using the same concentration these collapses did not occur.

#### DR S M LAIRD

Dr S M Laird said that, of about 80 adult females suffering from gonorrhœa—of which 11 were treated with 100,000 units—6, or 55 per cent, were cured, in that they had negative smears and cultures after 3 consecutive periods following treatment. One case treated with 150,000 units was cured. Of 23 cases treated with 200,000 units, 12, or 52 per cent, were cured, of 24 cases treated with 300,000 units, 18, or 75 per cent, were cured, of 4 cases treated with 500,000 units, 2, or 50 per cent, were cured, of 9 treated with 600,000 units, 77 per cent were cured, and 3 cases treated with 2,400,000 and a further 2 cases treated with 4,000,000 units were cured so he concluded that it was worthless to use penicillin in the female in a dosage of under 300,000 units, and that probably somewhere about 500,000 or 600,000 units was the optimum dosage.

The limited experience he had had with penicillin in the treatment of the complications of gonorrhœa had disappointed him. In cases of salpingitis the acute symptoms responded well, but a considerable number of patients remained with positive cervical cultures and smears, and many of the failures in the cases mentioned occurred in patients who had had salpingitis. He was interested in what Dr Mascall had said about vulvovaginitis. He had had the experience when he started his present duties, of inheriting 8 cases of vulvovaginitis which had been attending for 18 months and which had had frequent courses of a sulphonamide, and a number of courses of penicillin going up to as much as 800,000 units. He admitted them to hospital and gave them 1,200,000 units of penicillin, but without success. It was only after giving them œstrogen and following that up with small doses of penicillin that apparent cure had been effected. The surveillance period of these cases was about 4 months.

He had seen ophthalmia, not neonatorum, in one small child of about 2 years of age who also had vulvovaginitis, and although the response of the eye was dramatic, that of the vulvovaginitis was disappointing. He had only treated one baby with florid syphilis, and it had done extremely well. The twin of this baby was apparently healthy, and at 9 months still remained free from any symptoms of syphilis.

He had treated a number of cases of syphilis in pregnancy, and subsequently the babies appeared healthy and were serologically negative, but it was too early to draw conclusions. The response of tertiary lesions had been striking. The serological response in early syphilis was disappointing, it seemed to be slower than with arsenic and bismuth. His routine for the moment was 4,000,000 units of penicillin, together with 10 weekly injections of arsenic and bismuth, giving a total of 5.8 g.

#### MR AMBROSE KING

Mr Ambrose King said that he, too, spoke from impressions and had no figures to present. In regard to the possible effect of penicillin on the uterus, causing menstrual irregularities and perhaps abortion or premature labour, he had seen

a large number of women treated with penicillin and had not heard any complaints of or noticed any of these complications

On the question of the treatment of syphilis with penicillin, Dr Marshall had mentioned an argument which took place a year ago, and spoke of a "change of heart" as far as Mr King was concerned he was not aware of any change of heart. The treatment of early syphilis with 2,400 000 units of penicillin alone had produced excellent results, and none of the figures published so far had served to correct that impression. Until a large number of these case records were analysed it was unsafe to draw conclusions. It had been said that 85 per cent of patients with early syphilis would get well however badly treated and the other 15 per cent would give trouble however well they were treated. Perhaps the terms of this statement were too general, but it contained some truth and it was still not established that adding more and more arsenic or bismuth to the treatment with penicillin would reduce the number of resistant cases.

Mr King found it difficult to share the general optimism regarding treatment of gonorrhoea in the female with penicillin. He had had an opportunity of following most of the resistant cases of acute infection which Dr Mascall had mentioned and it was a fact that a percentage of cases treated with a large amount of penicillin failed to achieve bacteriological cure. He had been disappointed in the results in chronic infections also, because although bacteriological cure was apparently achieved, many of these patients showed evidence of residual infection, such as chronic cervicitis and symptoms and signs of pelvic infection. Pelvic infections, when acute often responded well to penicillin but many of these patients were seen afterwards with subacute relapses of their pelvic condition, and he doubted whether a substantial proportion of permanent cures was achieved by penicillin. Similarly with the metastatic infections of gonorrhoea such as arthritis, the relief of immediate symptoms such as pain and swelling was sometimes satisfactory but the end results were disappointing and he felt strongly that most of these patients required the addition of some form of fever therapy in order to achieve lasting results.

#### BRIGADIER T. E. OSMOND

Brigadier T. E. Osmond suggested that what had been said during the discussion was a great tribute to Dr Orpwood Price. The Whitechapel Clinic had had poorer results than most people in his view the more experienced pathologists would show up the failures better than the less experienced. The other point he would mention was the account in the *Journal of the American Medical Association* of a co-operative group which had been assessing penicillin and which had come to the conclusion that the present penicillin, which consisted of four factors F, X, G, and K, contained more K, which was relatively ineffective, apparently because it was so rapidly destroyed in the body. The group proved conclusively that the results

produced in syphilis up to May, 1944 were far better than the results since. It was interesting to note that they were now recommending for relapsed cases arsenic and bismuth in addition to penicillin—a method which had been used in this country for at least a year.

#### DR. DAVID NABARRO

Dr David Nabarro said that among the several points brought forward one of the most interesting was that pregnant women could be treated with penicillin alone and their children be born healthy. He thought it a very important observation because it did away with the risks of arsenical treatment, which were generally given as a reason against the treatment of all positively-reacting pregnant mothers. The point mentioned by Brigadier Osmond that the more penicillin was refined the less effective it became, was disconcerting either they would have to revert to the use of impure penicillin or find out the best fraction of penicillin and use that alone or combined with arsenic and bismuth.

In Dr Nabarro's view there was still too much congenital syphilis in existence. They knew how to prevent it and it was a disgrace that the disease still occurred. He went to the Hospital for Sick Children at Great Ormond Street London every Saturday, and frequently he was asked to look at a case of congenital syphilis. It had been found advisable, because of the shock reactions which sometimes occurred to begin the treatment with smaller doses than were usually recommended and he thought that treatment should be continued for at least 18 to 21 days. The total dosage, 170 000 units (Bodian, *Proc roy Soc Med* Aug 1945, p 572) should be spread out over 2½ to 3 weeks.

In American literature there had been several references to penicillin giving rise to abortion. Ingraham and his co-workers in America had recently again suggested that it has this effect. Goodwin and Moore on the other hand, concluded that they had not seen any case of it.

Dr Nabarro thought it must have been a coincidence that an infant did well with penicillin by mouth, because he would have thought the penicillin would be destroyed in the stomach.

When he was in charge of the clinic at the Hospital for Sick Children Great Ormond Street, he treated many of the children with bismuth alone and he found that one course of 12 injections of bismuth made the Wassermann reaction negative. He did not stop at that point, but repeated the courses of bismuth injections, and the patients seemed to have done well. He believed bismuth was a very valuable drug in syphilis.

To Dr Nabarro's question whether lumbar punctures had been carried out on the cases which Dr Morton had said were cured of syphilis with penicillin, Dr Morton said yes. Dr Nabarro said that he was constantly advising caution in claiming for penicillin more than it was capable of doing and he thought we must wait at least 10 years before saying that a patient was probably clear of the disease.

## LT-COL R R WILLCOX

Lt-Col R R Willcox understood that the new drug "Benadryl" was now coming into use in this country. In the United States this drug was showing very promising results in the treatment of urticaria occurring during penicillin therapy. Penicillin was also very effective in the treatment of secondary yaws. As far as the British Army was concerned there were published figures available for early syphilis showing that when 2,400,000 units of penicillin by itself were used there was an 8 per cent relapse rate at 6 months. It was hoped that later figures would soon be available.

Mr King asked whether it was not a fact that the published figures of 6 months' results were on 270 patients and not on the many thousands treated.

Col Willcox replied that the figure 270 referred only to those cases which it had been found possible to follow for 6 months at the time that particular estimate had been made. It had been drawn from many times that number actually treated. Such research in the Services was hampered by demobilization both of doctors and patients, but the Army was pursuing the investigations and it was hoped to have available further interesting figures shortly. The reference to the American article made by Brigadier Osmond was of great importance and might explain the differences of opinion between members as to the optimum dose of penicillin in the treatment of early syphilis. The article referred to information which came to light in America within a week of the United States Public Health Service conference on penicillin in syphilis held in Washington on Feb 7-8, 1946. This was that laboratory experiments had shown that the K fraction of penicillin was ten times less effective in rabbit syphilis than penicillin G, furthermore that recently the commercial penicillins had contained greater and greater proportions of penicillin K. A later analysis of results had shown a gradual decline in the efficacy of commercial penicillin since 1944. It would be interesting to know if similar factors were operating in this country.

## DR V E LLOYD

Dr V E Lloyd thought that the change in the efficacy of penicillin in America corresponded to a change in the method of manufacture. The deep tank method of production seemed to have produced a penicillin which did not give such good results in syphilis. The recent availability of penicillin in this country had depended on production from the deep tank method and he, and no doubt others, were a little uneasy as to the value of present-day penicillin. He had been assured by a representative of one of the manufacturers in Great Britain that the penicillin they produced contained very little penicillin K. It was penicillin K which had appeared in increased quantity in the American 'deep tank' penicillin, and which was reputed to be of no value in syphilis. He had no doubt that others like himself were apprehensive of this situation and would like to see it cleared up. Perhaps the

manufacturers would make some combined statement in the medical press on the present constitution of British-made penicillin.

There were several points in the discussion which had interested him. One was the account given by Dr Lees of the infant who was treated by the addition of penicillin to its feeds. Dr Lees seemed a little surprised at the excellent results, and further scepticism has been forthcoming in the discussion, but personally he thought it was an admirable way of treating a premature or recently-born syphilitic infant. There had been some work recently published\* which showed that the absorption of penicillin from the very young infant's stomach was very high, and that the blood level was adequate. In a few years it was likely that the treatment of very young infants with congenital syphilis would be by mouth or by the inhalation method by which penicillin was also absorbed very rapidly.

They had to think not only in terms of dosage of penicillin or method of administration, but also in terms of the relative accessibility of the various tissues of the body. A case of iritis was mentioned in which the results were poor, but that was what one would expect. The degree of penetration of penicillin into the aqueous or vitreous fluids of the eye was very slight, it was almost impossible to get more than a trace of penicillin into the eye by whatever method it was given. There was some hope that increased accessibility into the eye might be effected by the therapeutic production of increased vascularity in the eye. There was a pointer to this in the treatment of interstitial keratitis where the results of treatment with arsenic were better when it was given in the stage of high ocular vascularity. The treatment of joint disorders also was not very successful. The amount of penicillin reaching the synovial cavity was very small, and already physicians had started to treat arthritis by aspirating the joint fluid and then inserting the penicillin. These limitations had to be borne in mind when assessing the value of penicillin.

## MAJOR IRENE HOWARTH

Major Irene Howarth said that at her treatment centre, 30 cases of syphilis had been treated with 2,400,000 units of penicillin. There was considerable difficulty in following the patients up, owing to demobilization and also because many had left the area and attended other centres. One patient had been followed up for 18 months, 1 for 12 months, 3 for 6 months and 12 for 2 to 5 months, and all so far were satisfactory. More recently 28 cases of syphilis had been treated with 4,000,000 units and so far all attending the treatment centre were satisfactory though they had not been followed up for very long. These two series included 4 pregnant women who had had no disturbance of the pregnancy. These 4 patients were given arsenic and bismuth injections weekly after the penicillin course.

\*Henderson, J L., and McAdam, J W J. 1946 *Lancet* i 922

One of the 4 cases of double infection treated with 2,400 000 units of penicillin still harboured gonococci at the end of the course, subsequently, after a course of sulphathiazole all smears and cultures were negative. One mucocutaneous relapse was seen which had been treated at another centre in July, 1945, with penicillin (2 400 000 units) for a primary sore of the lip. The Kahn tests were negative in October and December, 1945, but in February of this year the Kahn was positive (20 units). Mucous patches were present in the mouth and there were many small vulval ulcers the serum from which contained *T pallidum*. This case was treated with penicillin 4 000 000 units and intensive mapharside therapy and so far the result was satisfactory.

Sixty consecutive cases of gonorrhoea were treated with 100 000 units of penicillin, and of these 19 had passed their final test of cure. There were 7 known relapses—3 positive before discharge from hospital, 3 positive at the first surveillance tests and 1 positive at the third surveillance test. 34 cases had not yet completed surveillance or had been demobilized. More recently 200 000 units of penicillin had been used for gonorrhoea and none of the cases had yet completed surveillance but all were negative immediately after treatment. Just over 50 per cent of her cases of gonorrhoea also had trichomonas vaginitis. The only complications of treatment with penicillin which she had encountered were 2 cases with intense urticaria and one girl who had extremely severe dysmenorrhoea.

#### DR. LETITIA FAIRFIELD

Dr Letitia Fairfield said that the last speaker and others had raised in her mind a problem which had not been mentioned and which was not directly clinical but which seemed to be of considerable importance. In connexion with the planning for a national health service she found that there was a tendency to assume that the social problem of infectivity especially in women was already solved by sulphonamides and penicillin, and that it was unnecessary to have any provision for what she might call the preventive type. In London and elsewhere, hostels had been established where women who were likely to expose themselves and others to the infection were encouraged to remain and where attention was paid not only to guarding them during the period of possible relapse but also to making a real endeavour to rehabilitate them and get them to adopt some other means of livelihood. She hoped that when members were being consulted on these matters they would remember these points: she felt that otherwise a very unfortunate position might arise because there was widespread misunderstanding about the position which treatment of venereal disease had attained. She felt strongly that they could not yet rely on out patient treatment only, and that the lay officials in whose hands their destinies so largely lay should not be encouraged to believe that out patient treatment was adequate for the prevention and cure of venereal disease.

#### DR. HEYWOOD

Dr Heywood said that with regard to Mr King's statement that he was satisfied with the penicillin treatment of early syphilis, he thought that Col Pillsbury's second paper published in the United States recorded that secondary syphilis treated with penicillin alone had an infectious relapse rate of over 20 per cent.

Mr King said he was referring to early syphilis generally. He did not say he was satisfied but on comparison he still considered it to be good treatment.

Dr Heywood said that, whatever might happen ultimately to patients treated with penicillin a high infectious relapse rate was alarming from the public health point of view.

His impression was that there was a great deal of unrecognized congenital syphilis but that they were only dealing with the few cases which came to light fortuitously. This was a blot on the antenatal services of the country: it could be wiped out completely by proper antenatal treatment.

On the question of follow up of female patients treated with penicillin for gonorrhoea the treatment had been made so easy that the patients defaulted earlier than ever. In his experience the early default rate was greater now than it was before gonorrhoea was treated with penicillin and also in his experience the administration of even a small dose of penicillin 100 000 or 150 000 units to a patient with gonorrhoea might delay the appearance of syphilis for as much as 3 months. The practice had been adopted that all patients must remain under observation for at least 6 months to make sure that concomitant syphilis had not been masked by the penicillin.

#### MAJOR WORDINGHAM

Major Wordingham spoke from the experience of a large number of male patients and to a lesser extent of female patients. He felt that the present tendency to neglect local therapy and to give penicillin alone was one of undertreatment. He treated all complicated cases of gonorrhoea in men with 150,000 units of penicillin together with 24 g. of sulphathiazole in 4 days. Female patients whose cases were notoriously complicated and who often attended only when the condition was well advanced were given 300 000 units combined with 24 g. of sulphathiazole.

Many venereologists would not face the fact that a large number of patients treated with a single or five multiple injections of penicillin alone, up to a total of 150 000 to 200 000 units had a recurrent urethral or cervical discharge. They were not cured. Too often the cases were diagnosed as non specific infections, when in fact they were relapses: he thought that this was due to inadequate initial therapy. They were deluding themselves in relying upon penicillin alone especially in the male with complications and in every female patient and this was also the experience of some of his civilian colleagues.

The routine treatment of syphilitic pregnant women of whom he had seen many recently

was 4 *mega* units of penicillin. For a fit woman he had combined this with 8 to 10 daily injections of 0.04 mg. of mapharsen together with 5 bi-weekly injections of 0.2 g. of bismuth. There had been no untoward reactions with this routine. The first baby had arrived and was perfectly healthy, the mother had had secondary syphilis.

In the treatment of early syphilis with 2.4 *mega* units of penicillin, the suggested relapse rate of 8 per cent was a little conservative, his experience would indicate a 20 per cent relapse rate within 6 to 9 months. No dangerous complications had been encountered during combined treatment of penicillin and intensive therapy with mapharsen. Even with that treatment he had seen 4 relapses and, therefore, he thought that primary sero-positive cases would do much better if bismuth was also given. In the Army it was possible to achieve this with 2.4 to 4.0 *mega* units of penicillin and 0.4 to 0.6 g. of mapharsen, together with 1 g. of bismuth. In civilian practice out-patients could be treated with daily injections of the oil-wax preparation, slightly lower doses of mapharsen, and bi-weekly bismuth. From his observation of the reaction of the soldier to this routine he thought that most civilians should be able to follow their employment. The absence of severe complications, such as dermatitis and encephalopathy, made him wonder whether the penicillin counteracted the toxic effects of the mapharsen in any way.

Had the gonococcal complement fixation test any value now? He did find it valuable as a test of cure, and often it enabled him to decide whether a case was one of relapse or reinfection. He had recently found the test positive in the majority of the cases that had failed to respond to the single injection treatment.

Mr King asked if he might make his point of view clear on the question of penicillin for early syphilis. He was not satisfied with the results with 2,400,000 units alone, and in his own patients he used arsenic and bismuth as well. At the same time there had not been a survey of a large number of cases which proved beyond question that the 2,400,000 units was unsatisfactory, and it was wrong to form ideas on a few scattered impressions, or on the unsatisfactory experiences of a few people with few cases. It was necessary to have an investigation on a large number of cases.

#### DR BURGESS

Dr Burgess supported contention that better results were obtained in the treatment of early syphilis by using penicillin together with arsenic and bismuth. He had been giving 500,000 units daily for 10 days with a full course of neoarsphenamine and bismuth, and so far he had not seen any relapses. There had been two cases of urticarial rashes, and one case developed acute angioneurotic oedema. In cases of gonorrhoea, better results were obtained by giving concurrent sulphathiazole, 25 g. in 5 days and an initial injection of 250,000 units of penicillin.

He also had had the experience reported by Dr Marinkovitch, that the vaginal discharge did not clear up. Many patients said that the discharge

was worse after penicillin. In his view most of these cases would be found to have a concurrent trichomonas infection, and unless this was treated also the results from the patient's point of view would be very poor. He did not know whether the penicillin encouraged the trichomonas, but he had found positive specimens more frequently after penicillin than before.

On the question of cultures it might be that the medium used was not so good as in other places, but he had never had a positive culture unless it had been grown in 8 per cent carbon dioxide, plain cultures gave negative results. By using this method he had obtained many positive cultures where the smears had been negative.

#### MAJOR BETTY WALKER

Major Betty Walker said that unless trichomonas infestation was treated simultaneously with gonorrhoea good results would not be obtained. She wondered whether the reason that some speakers did not attain good results was that the trichomonas vaginitis or concurrent cervicitis had not received local treatment at the same time.

#### MAJOR SCOTT

Major Scott said that he had noticed that gonorrhoea patients treated by him had been returning 5 or 6 weeks after treatment by penicillin with considerable urethral discharge, in which pus cells, with gonococci and other organisms, were present. Further examination showed the presence of a hazy urine. A large proportion of men were failing their final tests of cure. Examination showed a great number of pus cells in the prostatic bead. He thought that it might be a wise procedure to examine the prostatic contents some 4 or 5 weeks after discharge from hospital, so that further treatment, if necessary, might be given at an early stage.

Major Scott had recently seen a case of secondary syphilis that had been treated in Germany some 3 months previously with 2,400,000 units of penicillin. The clinical condition had been little improved, and a florid maculo-papular eruption with associated laryngitis was still present.

With regard to gonorrhoea, he thought that possibly the best results he had seen were in cases in which penicillin had been combined with sulphathiazole. Abroad he had been using penicillin, 140,000 units, combined with 15 g. of sulphathiazole. On the first day the patient received 7 injections, each of 20,000 units of penicillin, together with 4, and thereafter 2, tablets of sulphathiazole. On the second day sulphathiazole was given alone, in 7 further doses of 2 tablets. He believed that this treatment gave a high rate of incidence of cure.

#### DR G L M McELLIGOTT

Dr G L M McElligott (the President) thought the reason why penicillin had not been used alone in civilian practice was, first, shortage of beds and, secondly, unreliability and shortage of supply of drugs.

When evaluating treatment by penicillin and arsenic and bismuth, it was necessary to bear constantly in mind that a minimal amount of arsenic-bismuth treatment would cure many cases of early syphilis. Most would agree that about 5 g. of neoarsphenamine and 2 g. of bismuth in one course would cure between 60 and 70 per cent. of cases of early syphilis. They were told that 15 per cent. of all cases of early syphilis could not be cured, and it had to be borne in mind that 20 per cent. of cases of early syphilis, even if not treated, would ultimately cure themselves, which did not leave much margin for evaluating the penicillin. In all cases of syphilis early or late, with the possible exception of advanced and gross cardiovascular syphilis, penicillin was indicated. He thought they must make up their minds to give it to all cases of syphilis in addition to any other treatment they felt the patient should have. The place of penicillin in the treatment of syphilis had not yet been determined and it would be a long time before it could be so determined, but it was a powerful anti-syphilitic drug; it was comparatively harmless and why should it not be used?

With regard to gonorrhœa the results which a great many of the speakers had reported were rather depressing. It might be that there was too much of penicillin K in the preparation but that was not known. What was significant was that the dosage of penicillin seemed to be rising for the treatment of gonorrhœa. They used to talk about 100,000 units 18 months ago, and now they were talking about 300,000 units. It might be that the gonococcus was getting used to it, and now that it was likely that every case of tonsillitis would in future get a shot of penicillin

from the doctor he thought they would have to watch for real trouble.

The follow up of gonorrhœa cases was very important and he thought it should be more detailed even more than prolonged. During the first fortnight and three weeks they needed to see female patients almost every second day. The giving of a few shots of penicillin and saving

Come back after the next period, was inadvisable. After the first three weeks one had a good idea of what was going to happen. He thought that local treatment was necessary. Gonorrhœa in the female was a mixed infection. The infected and abraded cervix was in contact with a potentially septic vagina, and organisms which did not have the ability to penetrate healthy mucous membrane could flourish upon an unhealthy mucous membrane. The coincidental trichomonas infestation seemed to be getting more and more common, and his own practice was to advise a douche while giving the penicillin and for a week after, in the hope that such cervical discharge as was in the vagina would be washed away and the vagina would not be reinfected.

He thought that to give sulphonamides as well as penicillin was good practice but he did not agree with treating cases initially with sulphonamides and only treating the failures with penicillin. The great point about penicillin was that one knew that the patient was getting the treatment with sulphonamide treatment in women how often was regular medication carried out? The dosage of penicillin seemed to be arbitrary but as far as women were concerned it was getting very near if not up to, 300,000 units. He had seen 2 cases of inter-uterine bleeding in six months and one of these cases actually aborted.

# LOCAL PENICILLIN IN LYMPHOGRANULOMA INGUINALE

BY

G O MAYNE and A D BAIN

Most observers agree that penicillin is of little benefit when administered systemically in cases of lymphogranuloma inguinale, though Willcox (1946) reports good results in 2 patients. The following case would suggest, however, that penicillin may prove of value when administered locally in this condition.

## Case History

The patient, a European male aged 30 was admitted with the complaint of a painful swelling of 1 week's duration in the left groin. He had no past history of venereal disease, but admitted sexual exposure with a native woman 2 weeks before admission, and also several months previously.

On examination he was found to have a tender, indurated, non-fluctuant swelling of the left inguinal glands, with redness of the overlying skin. There were no penile sores, no scars, and no urethral discharge, and the urine was clear. He was also found to be infested with pediculi pubis but no cutaneous lesions were found in the genital area or on the lower left limb to account for the adenitis. No Frei test antigen was available for confirmatory diagnosis, but clinically the condition presented all the features of the adeno periaadenitis typical of lymphogranuloma inguinale.

Treatment was as follows:

No of  
days in  
hospital

- |    |  |
|----|--|
| 1  | Course of sulphanilamide started (5 g daily for 5 days) with injections of anthiomaline (2 c cm on alternate days)             |
| 5  | Course of sulphanilamide completed. Anthiomaline continued.  |
| 11 | Glands fluctuant. 5 c cm of viscid pus aspirated. Laboratory report: smear, pus cells +, no organisms, culture sterile.        |
| 12 | A further 7 c cm pus withdrawn.  |
| 17 | Overlying skin broke down, leaving an abscess cavity with undermined edges. Anthiomaline continued. Flavine dressings locally. |
| 24 | No improvement. Anthiomaline continued. Eusol and sulphanilamide powder locally.   |

No of  
days in  
hospital

- |    |   |
|----|---|
| 28 | White blood count 5,000/c mm. Course of sulphamethazine started (5 g daily for 5 days). Anthiomaline continued.   |
| 40 | Anthiomaline discontinued. Brilliant green locally.   |
| 42 | No improvement. Magnesium sulphate dressings locally.   |
| 54 | Further culture of pus from sinus revealed <i>Staphylococcus aureus</i> only. Ultra-violet light therapy instituted. Mercury perchloride 1/4,000 locally. |
| 66 | No improvement.   |
| 68 | Penicillin solution (1,000 units per c cm) applied locally by means of a dropping pipette.  |
| 82 | Almost healed.  |
| 85 | Fit for return to full duty.  |

Whether the *Staphylococcus aureus* found in the pus from the sinus was an actual factor in retarding the process of healing or was present merely in the role of secondary contaminant is uncertain, but the response to penicillin applied locally was dramatic. At the present time the site of the sinus is completely healed and scarring is minimal.

Further satisfactory results have been obtained by us in two other European patients following the injection of penicillin in identical strength through the same needle left *in situ* after aspiration of the abscess cavity.

## Summary

A case of lymphogranuloma inguinale is described which responded immediately to local penicillin therapy after two courses of sulphonamide drugs, one course of 14 injections of anthiomaline, repeated sessions of ultra-violet light irradiation, and a large variety of local antiseptics had failed to produce any appreciable improvement.

We wish to thank Lt-Col. W. N. J. Clarke, OBE, Officer Commanding a military hospital, for permission to publish this note.

## REFERENCE

Willcox, R. R. (1946) *Brit J Venere Dis*, 22, 63

# ACUTE ENCEPHALOPATHY AND ARSENOTHERAPY OF SYPHILIS

BY

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Acute hæmorrhagic encephalitis or encephalopathy is, perhaps, one of the most dreaded of complications which can occur during arsenotherapy of syphilis. Before the introduction of intensive arsenotherapy by Chargin and others (1935), the incidence of this condition was almost negligible, according to Harrison (1939), only 8 cases were reported from 800,000 injections during the war of 1914-18. Since the popularization of intensive arsenotherapy during the world war 1939-45, however, the incidence of encephalopathy has increased considerably. Its incidence varies according to different workers: thus Young and Gordon (1944) report 5 fatalities from acute encephalopathy following about 10,000 injections at an East African Centre, the drug used being neoarsphenamine, 0.6 g twice weekly, in addition to 2 weekly injections of bismuth metal of 0.1 g each. Lydon (1944) reports that 5 out of 53 patients developed the condition during treatment by a short-term intensive course of mapharside, one of his patients died. Pillsbury and others (1944) state that the reaction of encephalopathy did not occur frequently during intensive arsenotherapy by a modified 20-day treatment. Lloyd Jones and Martland (1945) report 3 cases out of a total of 241 (?) patients treated by a modified course of intensive arsenotherapy.

According to McDonagh (1920), the condition develops some 48 to 72 hours after the second or third injection. Pillsbury and others, quoting U.S.A. Army circular letter No. 138 on intensive therapy for early syphilis, say that it is characterized by 'mild to severe mental confusion, headaches, fever, convulsive seizures, and in some cases coma. Spinal fluid sometimes shows marked increase in protein'. The treatment most generally adopted is venesection, lumbar puncture, intravenous hypertonic glucose, and the administration

of adrenaline or benzedrine, but the results of treatment have varied (McDonagh, 1920; Young and Gordon 1944; Lydon, 1944). The use of thiosulphate, intravenously, has also been advocated (Sheppe, 1930).

Lydon (1944) brings out several points of interest and importance which do not appear to have been noted by other workers. In his series of cases he observed that the primary signs of encephalopathy occurred in the mental sphere, either as a sudden explosive onset of acute apprehension and fear, or as a general slowing of cerebration. The resemblance of these mental changes to those of the two types of alcoholism led to a tentative suggestion that perhaps a similar pathological condition was present and that the condition might be avoided or improved upon the exhibition of vitamin B<sub>1</sub>. Alcoholism is suggested as a predisposing factor. Upon this hypothesis vitamin B<sub>1</sub> was administered in the later cases of the series quoted, with apparently marked benefit. The following case is of interest in the light of Lydon's observations.

## Case History

The patient was a male aged 24 years who was referred for examination on Sept. 22, 1944, for a possible syphilitic infection. He was undergoing treatment for co-existent scabies and gave a history of exposure to infection in the previous March. He stated that in March 1944, following exposure, he had developed a urethral discharge which had been treated with sulphathiazole. He had had a penile swelling since the following May or June and was using calamine lotion locally. He was suffering from malaise and was sleeping poorly due to the irritation caused by the scabies. He admitted to fairly heavy alcohol consumption up to 3 or 4 weeks before examination.

On examination there was penile swelling, marginal ulceration and induration of the prepuce, marked enlargement of the inguinal glands and superficial ulceration of the right tonsil with redness of both tonsillar regions. There was an



indefinite secondary rash confined chiefly to the lower abdomen, though it was difficult to be certain about this on account of the superimposed scabies

Due to the local treatment, *T pallidum* was not definitely demonstrated on the first examination but was found on the patient's next reporting on Sept 25. Treatment was begun on the same day, when 0.04 g mapharside in sodium thiosulphate solution was administered intravenously. On Sept 27 and 29 and on Oct 2, 0.06 g mapharside were given, together with 0.1 g bismuth on each day. The patient lived in the country and returned home after each treatment. Several days after the fourth injection his doctor telephoned to say that the patient was confined to bed with influenza and was unable to come for further treatment meantime, his doctor was not alarmed about his condition. On Oct 7 a further message reported that the patient was still ill but his doctor was still not unduly alarmed, but on Oct 9 his condition was reported to be much worse and he was now delirious. Personal difficulties had delayed his earlier hospitalization, but it was obviously impossible to treat him by directions by telephone. Admission to hospital was urged and he was admitted the same evening.

A more coherent history of events was now obtained. He had gone to bed on account of a "cold" following his last injection, by the next day his temperature had risen to 103° F. He remained in bed, and his high temperature continued until Oct 6, when it fell to 99° F, when his condition improved somewhat, but on Oct 8 he developed convulsive fits and became comatose 5 or 6 hours later. The coma lasted until the early hours of the following morning. He had been lethargic and had taken very little food or liquids since his return home on the day of his last injection.

On admission to hospital, he was in a very excitable state and was shouting and struggling. He was quite unconscious of his surroundings and unable to recognize his mother. He appeared to be very apprehensive of all that was happening and made violent efforts to get out of bed, being restrained with considerable difficulty—so much so that clinical examination was extremely difficult and unsatisfactory. There was a divergent strabismus of the left eye, marked neck rigidity, and a positive Kernig's sign. He was incontinent.

Further examination or interference were impossible for several hours, when a lumbar puncture was performed with some difficulty. About 20 c cm of clear cerebrospinal fluid was withdrawn and was reported on as follows: protein 120 mg per 100 c cm, chlorides 700 mg per 100 c cm, globulin increased, cells 20 lymphocytes per c mm.

Further treatment consisted in the intravenous administration of 50 c cm of 30% dextrose and 20 c cm calcium gluconate. On Oct 10, by nasal feed at 4 a.m. he was given 2 pints of glucose and sedatives. Large quantities of fluids were given. Fluids were forced. The patient was still very noisy and difficult to restrain in spite of sedatives. On Oct 11 he was drowsy and quieter. When awakened for drinks, his eyes and face were quite expressionless.

By Oct 12 he was somewhat brighter and was attempting to speak, but articulation was difficult, his face was still expressionless. He recognized his mother. On Oct 13 he was more normal and was able to talk and take food. He asked to be changed to another ward with other patients, as he said there was a tall, dark man behind the curtain who kept looking at him during the night. (There was no curtain in the ward.) On Oct 14 he had a good night. He was bright and talkative during the day and was taking food normally.

Subsequent progress was uneventful. A lumbar puncture on Oct 21 showed protein, 40 mg per 100 c cm, globulin negative, chlorides, 670 mg per 100 c cm, cells, 10 lymphocytes per c mm.

Most authorities agree that further exhibition of arsenicals is absolutely contraindicated after a crisis of the type described. Unfortunately, penicillin was not then available and we were faced with the alternatives of either continuing treatment with bismuth or of risking a further cautious dose of an arsenical preparation. Here was a man, 24 years of age, who had had inadequate treatment for secondary syphilis, and who was now faced with the alternatives either of inadequate treatment of a very serious condition, with all the dire possibilities consequent thereon, or of the risk of further arsenotherapy. It was considered that, taking a long view, a further cautious dose of mapharside should be tried.

His general condition was now much better than it had been at the beginning of treatment, and he had shown no evidence of further mental reactions. On Oct 23 an injection of 0.02 g of mapharside in high dilution and containing 0.45 g thiosulphate was given very slowly intravenously. About 2 hours after the injection the patient's face became flushed, his eyes became slightly injected, and he developed a headache which lasted until the next morning. On Oct 24 it was decided to start injections of vitamin B<sub>1</sub>, and daily thereafter until his discharge from hospital on Nov 16, 1944, he was given an intramuscular injection of 5 mg of thiamine hydrochloride.

On Oct 30 a further injection of 0.02 g of mapharside was given, with the same precautions as before. About 4 hours after the injection, the patient's face became flushed, his eyes injected,

and his body warm, but the reaction was not only much less than before, but it lasted only 4 to 5 hours. There was no headache. On Nov 5 he was given 0.03 g. of mapharside as before and this time he had a slight feeling of warmth which lasted for a few minutes only. On Nov 13 after 0.04 g. of mapharside given with the same precautions he had no reaction whatsoever.

Between Nov 27 and Dec 20 1944, after his discharge from hospital, the patient had 4 injections of 0.04 g. mapharside without further untoward reaction. During the following 12 months he had 2 further courses of treatment, each consisting of 10 weekly injections of 0.04 g. mapharside and 0.1 g. bismuth. During the first of these courses thiamine hydrochloride was given daily intramuscularly, and during subsequent treatment oral vitamin B therapy was administered. There was no further reaction of import during treatment, and his blood Wassermann and Dreyer reactions have remained negative for some time. He is still under periodic observation.

### Discussion

It is difficult to draw conclusions from a single case, but when the condition is comparatively rare the observed reactions in individual cases become of considerable importance. The case described would appear to bear out at least some of the conclusions reached by Lydon (1944). Unfortunately, circumstances prevented personal observation of the symptoms during the onset of the condition, but from what was learned subsequently the onset seems to have been rather of the lethargic type as described by Lydon. Most workers are agreed that the first 3 or 4 injections during arsenotherapy should be given over a period of some 10 to 14 days, and the treatment in this case was not out of harmony with recognized practice. The clinical findings and the result of lumbar puncture were like those described in other cases of similar type. Lydon (1944) points out that Kernig's sign was not a feature of his cases, and suggests that, in the single case he noted, the sign was probably one of nuchal rigidity. This may have been so in the patient described in this paper.

The chief point of interest in the case described is the response to treatment following encephalopathy. It was an admitted risk to

recommence arsenotherapy, but the circumstances governing the decision to do so have already been discussed. In retrospect it would seem that perhaps an even smaller trial dose of the drug should have been administered. The reaction to the first injection of mapharside after encephalopathy, and the rapidly decreasing reactions following the second and subsequent injections on the exhibition of vitamin B<sub>1</sub>, would seem to bear out Lydon's theory about the importance of this vitamin in the prevention of arsenical encephalopathy.

The advent of penicillin for the treatment of syphilis brought with it high hopes that arsenical encephalopathy would be a thing of the past. It is now, however, becoming more generally realized that the best therapeutic results in the treatment of syphilis with penicillin are to be obtained, not with penicillin alone, but by combining penicillin with the older established methods of treatment. Some workers (e.g. Pillsbury, 1946) advocate a short intensive course of arsenotherapy with penicillin. There is thus still the possibility of the occurrence of encephalopathy, and the use of vitamin B<sub>1</sub> in its prevention or treatment is worth further investigation. Alcoholism may also play a part in the causation of the condition.

I am indebted to Surgeon Commander Hugo Hall, R.N.V.R. Director, V.D. Clinic, Royal Victoria Hospital, Belfast, for criticism and advice and to Dr F. Kane, Medical Superintendent, Purdysburn Fever Hospital, Belfast, for help during the early days of the patient's illness.

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## CORRESPONDENCE

*Letters are welcome on all matters of general interest. Publication does not necessarily imply that the Editor agrees with the views expressed*

### ARSENICAL ENCEPHALOPATHY

Sir,—In his interesting article on the above subject, which was published in the *Journal* for September and December, 1946, pp 93 and 139, Dr E E Prebble said (p 100) "The Salvarsan Committee expresses the opinion that the condition is really an acute cerebral syphilis, intensified as a result of the injection, but they do not give any evidence which really supports this view." I was a member of the Salvarsan Committee, and am very conscious of the fact that, if such a theory had been advanced there, I should have opposed it strenuously. Accordingly I have waited for Dr Prebble's list of references before writing to you on the subject. Dr Prebble's reference is to the Medical Research Council's Special Report No 66, on p 22 of which appears the following

*"Pathology of Encephalitis Haemorrhagica"*

"Two views have been held with regard to the aetiology of this very fatal complication (1) that it is really acute cerebral syphilis, intensified as a result of the injection (Herxheimer reaction), (2) that it is the direct result of the salvarsan, possibly in persons unduly susceptible to the drug

An examination of the literature of active syphilis in pre-salvarsan days does not lend support to the first theory. Add to this the fact that no spirochaemes can generally be found in the cerebral tissues, and a strong case against the condition being regarded as acute cerebral syphilis begins to be built up.

The probabilities of salvarsan being the direct cause appear very great."

To me it appears that the view of the Salvarsan Committee that arsenical encephalopathy is *not* due to cerebral syphilis, intensified by the injection, could not have been expressed more clearly.

Unfortunately, this letter must appear some months after the original statement, and I apprehend that, in consequence of the latter, in years to come many a critical review on toxic effects of the arsphenamine group of remedies will mistakenly attribute to the Salvarsan Committee the view that arsenical encephalopathy is due to cerebral syphilis.

I am, etc,

L W HARRISON

London S W 1

## BOOK REVIEW

### *AN ATLAS OF THE COMMONER SKIN DISEASES*

By Henry C G Semon, M A, D M, F R C P,  
with photography directed by Arnold Moritz,  
M A, M B, B Ch

(Bristol John Wright and Sons Ltd 1946 Third  
Edit Pp 343 with 139 Coloured Plates  
Price 50s net)

It is recognized that dermatology can be learnt successfully only by attendance at a skin clinic, where the differential diagnosis can be considered in relation to the actual patient. Dermatology is perhaps unique in this respect, for in no other branch of medicine is the visual memory so essential to a full understanding of a particular disease. However, Semon's Atlas has for twelve years been accepted as a supplement in which the common diseases can be shown to the student when required, whereas the typical patient will never appear when he is most needed. The Atlas has already gained a wide popularity with the

student, who so frequently finds the subject especially difficult to grasp and many practitioners have come to refer to it for assistance in obscure cases when no expert advice is available.

The high standard of the publication has been fully maintained in this third edition, in spite of the many difficulties of production which exist at the present time. Many additional plates have been added, and the descriptive details have been expanded. The colour reproduction is generally excellent, although plates 11, 18, 43, 47, 52, and 78 are below the average standard. It is clear that considerable care has been taken in the selection of cases suitable to illustrate the characteristics of the various diseases, but the diagnosis of the cases shown in plates 42, 45, 96, and 101 appears from the photographs to be debatable, and plate 125 is not convincing. Nevertheless, this enlarged new edition is a commendable achievement which reflects credit on both the authors and publishers, and there can be no doubt of the success which it will attain.

D E

## ABSTRACTS

(The abstracts are divided into the following sections syphilis (general) penicillin in syphilis gonorrhoea general After each subsection of abstracts follows a list of articles that have been noted but not abstracted)

### SYPHILIS (GENERAL)

Carriers of Syphilis (Les porteurs de germes syphilitiques) BESSEMAN, A and VERCOULLIE, J (1946) *Brux med*, 26, 1133

*Treponema pallidum* can live as a saprophyte on the body surface for some time before it accomplishes penetration, and this may account for certain cases with an extraordinarily long incubation period. People with serological evidence of syphilis but with no clinical signs of disease have often been proved contagious. *T. pallidum* has been demonstrated in cervical secretions of women showing no sign of disease but who have been in contact with men with florid syphilis. The organism has also been found in the lymph nodes of latent syphilitics.

Cases of contamination by syphilitics showing no surface lesions or serological evidence of disease have often been described—as by the bite of a patient with general paresis (positive evidence in the cerebrospinal fluid). People incubating syphilis can spread the disease. [This is a most important point which is often insufficiently stressed.] The blood may be highly contagious at any stage, and this bears no relation to the reaction of the serum.

Three cases are cited. (1) A woman was living with a man who was found accidentally to have a positive Wassermann reaction. The woman gave no history and showed no signs of syphilis and serum tests were negative. She was accused of being the source of infection in the case of another man with whom she had intercourse 5 weeks before the start of investigations in her case and who developed a chancre 16 days after coitus. (2) A prostitute under supervision every fortnight over 3 years had been in hospital 4 times in this period; fortnightly serum tests over several months gave negative results free from any evidence of syphilis. She was accused of infecting a man with syphilis coitus having taken place several days before her last (negative) serum test was made. (3) A prostitute was under fortnightly control with frequent serum tests over 3 years and 4 months showing no evidence of syphilis. Three times in this period at intervals of 4 and 15 months she was accused of having transmitted syphilis to men. The infected men in these cases all denied the possibility of any other source of contamination. In case (2) the woman still showed no evidence of disease some

months later. Seminal transmission of *T. pallidum* is suggested as the most likely method in case (1).

The absence of syphilis in these cases may be explained by a natural local immunity or by an immunity acquired by repeated contact with *T. pallidum*. [Janet (*Diagnostic et Traitement de la Blennorrhagie*) suggested that prostitutes after many attacks of gonorrhoea, eventually develop a certain immunity.] Rabbits and mice were inoculated with cervical secretions from these women but no syphilomata developed in the rabbits and lymph node transfers (4 to 5 months later) from both the rabbits and the mice produced no lesions in rabbit testicles. These experiments suggest that the infecting agent had disappeared from the genital tract between 1 and 2 months after the suspect coitus.

Other articles are cited in which persistence of *T. pallidum* in the vaginal or other secretions for varying lengths of time has been noted. The authors conclude that there is a strong probability that *T. pallidum* may in certain women, be a true saprophyte and that such women may simply act as vectors.

[Although there is no reason to deny the possibility of the existence of carriers of syphilis the cases cited are not convincing. The article is interesting in its exposition of the infectivity of syphilis at various stages and in various ways.]

James Marshall

Physicopyrexia and the Biologic Healing of Early and Late Syphilis of the Rabbit BESSEMAN, A and DENOO, A (1946) *Arch. phys. Med.* 27, 547

An investigation was carried out on rabbits 154 of which were infected with the Ghent strain of syphilis. The decision was taken to combine chemotherapy and artificial pyrexia, since it seemed possible to obtain better results in this way than with either method separately. In some animals the disease had lasted 4 months (early cases) in others from 6 to 16 months (late cases). Three groups were chosen: one was treated by arsphenamine only, the second by artificial pyrexia only, and the third by both together. The arsphenamine was given in the form of a 10% solution of solusalvarsan; 3 intramuscular injections of 0.25 or 0.5 ml per kilo of body weight being employed at 3- or 8-day intervals. Artificial pyrexia was induced with the rabbit wholly inside a wooden cabinet, the air in which was heated

electrically and kept moving by a fan. The inductortherm cable was wound round the outside of the incubator, the rabbit thus lying within the electromagnetic field. In other cases the rabbits' heads were allowed to protrude from the incubator. These treatments were given at 3- to 8-day intervals. Temperatures of 42° C were attained for 30 to 60 minutes and 41° C for 2 hours. The rabbits in the third group were treated by both arsphenamine and pyrexia, the latter being induced either on the same day as, or on the day after, the injection. In all, 92 rabbits survived treatment.

Three tests of cure were employed: (1) testicular implantation into a normal rabbit of popliteal lymph nodes from an infected rabbit, (2) transplantation of an emulsion made from various organs of the infected rabbit, (3) re-inoculation of a previously infected rabbit with a homologous strain of *Treponema*, to determine whether a fresh syphiloma formed. Evidence of re-infection suggested previous complete cure. Great stringency and thoroughness were shown in evaluating the results: the types of reaction and the temperatures reached at various parts of the body are explained diagrammatically. The percentage cured was as follows:

	Arsphenamine alone	Pyrexia alone	Combined treatment
Early cases	60%	54%	100%
Late cases	25%	27%	83%

Injectations acted best when given just before the pyrexia, over 95% of the animals being cured as opposed to 75% when the injection was given afterwards. The authors attribute this success with the combined treatment to pyrexial stimulation of the natural defences, and show reason for hoping that combined therapy in human syphilis will bring about actual healing rather than mere masking of symptoms.

J H Cyriax

**The Value of the Quantitatively Standardized Complement Fixation Test in the Diagnosis and Treatment of Early Syphilis** MAILLARD, E R, and ORZEL, A. *Amer J Syph*, 30, 490

The results are given of quantitative complement-fixation tests in 693 patients with early syphilis treated with penicillin. Specimens were taken immediately before and after treatment, and then at weekly and, later, at monthly intervals. Over a period of 10 months 4,883 specimens were tested. The 693 patients included 196 with primary and 497 with secondary syphilis, 44 of the primary cases gave negative reactions before treatment, but 17 of these showed a weak reaction after treatment. Of the primary cases 50% showed no reaction with lesions less than a week old, 25% with lesions to 2 weeks old, and 5% with lesions from 2 weeks old; no negative reactions were obtained when lesions had been present for

4 weeks. Of the patients with primary syphilis 83% had titres of less than 50, whilst 93% of the secondary cases had titres of over 50. The highest titre in a primary case was 150 and in a secondary case 630. Of the 693 patients 325 were followed up for 3 to 10 months, 211 (87 primary and 124 secondary) showed a uniform drop in titre—when the initial titre was between 10 and 50, 3 months were required for the titre to fall to 8, when it was greater than 50, 3 to 6 months were required. The relapse rate was high since the dosage of penicillin varied from 60,000 to 600,000 units. Relapses occurred in 20% of the primary and 43% of the secondary cases, and 85% of relapses appeared within 6 months. Mucocutaneous lesions were found in 70% of patients showing serological relapse. It is concluded that this quantitatively standardized complement-fixation test is of great value in diagnosis, prognosis, and the control of treatment.

[The technique of this test is complicated and requires first-class pathological facilities. When the test is simplified it may be suitable for general use.]

T E Osmond

**The Treatment with Massive Arsenotherapy of Early Syphilis Complicated by Pregnancy** CURTIS, A C, and MORROW, G (1946) *Amer J Obstet Gynaec*, 52, 284

It is claimed that massive arsenical therapy offers a rapid and efficient method of treating syphilis in pregnancy. The results of Jeans (*Amer J Syph, Gon Vener Dis*, 1919, 3, 114) and of Marshall (*J Amer med Ass*, 1934, 102, 503) show the high incidence of stillbirth, abortion, and infant mortality when pregnant women with latent syphilis are untreated. The results of Marshall, McKelvey, and Turner (*J Amer med Ass*, 1934, 102, 503) show that the foetal prognosis is proportional to the adequacy of antenatal anti-syphilitic treatment. The good results of Sudusk and Shaffer (*Yale J Biol Med*, 1942, 14, 34), Rattner (*Amer J Obstet Gynaec*, 1943, 46, 255) and others with massive arsenotherapy by the 5-day drip method are recorded. The authors give their own results in 30 cases treated by the total injection of 1,200 mg of mapharside with 260 mg of bismuth. They then describe the treatment of 10 cases by a modified technique, in which a total of 1,080 mg of mapharside in 5% glucose was given intravenously by daily injections, with the associated administration of 4 doses of 130 mg of bismuth subsalicylate in oil intramuscularly. Liver and renal function were tested, and a blood count was made before treatment was begun. Neither abortions nor stillbirths occurred in this series. The fallacies of the testing of cord blood, of the Wassermann test, and of examination of the placenta, and the value of dark-ground examination of serum from the umbilical vein or infant's skin, are emphasized.

J Stallworthy

**Clinical Surgery and the Serodiagnosis of Syphilis** (Clinica y serodiagnostico de la sífilis) GARRIDO QUINTANA, F (1946) *Actualid méd*, 22, 516

**Modern Treatment of Syphilis** THOMAS, E. W (1946) *Amer J publ Hlth*, 36, 1002

**Results of Rapid Treatment of Early Syphilis** HELLER J R (1946) *J Amer med Ass* 132, 258

**Syphilis in Army Separates** ROSENTHAL, T and SOBEL, N (1946) *N Y St J Med*, 46 2042

**Should Cardiovascular Syphilis be treated Antisyphilitically?** (Bor syfilitiske Hjerter-Karledelser behandles antisyfilitisk?) BUCH H (1946) *Ugeskr for Laeg* 108, 1106

**The Kline Reaction for the Serodiagnosis of Syphilis** (Sobre la reacción de Kline para el serodiagnóstico de la sífilis) CARGO VILLEGAS A and GARRIDO BLANCO, A (1946) *Laboratorio*, 2, 221

**A Case of Syphilitic Meningo-Encephalomyelitis** (Su di un caso di meningo-encefalo-mielite luetica) BUTTARO C A (1946) *Rass int Clin Terap*, 26, 297

**Tertiary Syphilis of the Pharynx.** (Fall av tertiärlues i avalget) BRANTEFORS G (1946) *Nord Med* 31 2065

**Two Anniversaries in the History of Syphilis Research** (Zwei Gedenktage der Geschichte der Syphilisforschung.) HOFFMANN, M (1946) *Arch Derm Syph, Berlin*, 186, 93

**Intolerance and Effects of Arsphenamines in Syphilis** (Intoleranz und Wirkung der Arsenbenzole bei der Syphilis) TRUFFI M (1946) *Arch Derm Syph, Berlin*, 186, 54

**Syphilis in Pregnancy** (Sífilis en el embarazo) MESA RAMOS J D (1946) *Bol Soc cubana Derm Sif* 3, 97

**A case of Syphilis of the Stomach** (Bir mide sífilisi vakası) BILHAN, N (1946) *Türk Tip Cem. Mec*, 12, 201

**Anti syphilis Treatment** (Die antiluetische Kur) ROTTER, H (1946) *Wien klin Wschr*, 58 631

**Today's Treatment of Syphilis** O LEARY P A and KIERLAND, R R (1946) *J Amer med Ass*, 132, 430

#### SYPHILIS (Kahn Reactions)

**The Verification of Kahn Reactions** (Le reazione di verifica della reazioni di Kahn) DE FILIPPIS V (1946) *G Clin med*, 27, 524

**Simplification of the Kahn Reaction.** (Simplificación de la reacción de Kahn) LAZO GARCIA, S (1946) *Hispalis med* 3 345

#### PENICILLIN IN SYPHILIS

**The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis** EAGLE H, MAGNUSON, H J and FLEISCHMANN, R (1946) *Bull Johns Hopk Hosp*, 79

The curative dose of sodium penicillin in rabbit syphilis has been found to be affected by the number of injections given the greater the number the less the total amount of penicillin needed for a cure, though no appreciable difference is noted if these injections are given 4-hourly or twice or once daily

Nearly 350 rabbits were inoculated intratesticularly with Nichol's strain of *Treponema pallidum*, and treatment was started after the development of testicular syphilomata 5 to 7 weeks later. Thirteen different schedules with intervals between injections of 15 minutes to 4 days, the number of injections varying from 4 to 50 and the duration of treatment from 3 hours to 16 days were used. On each schedule from 3 to 9 rabbits were treated with commercial penicillin at each of 3-7 dosage levels. Cases where spirochaetes were still present 72 hours after treatment, or where they subsequently reappeared, were regarded as failures.

In rabbits injected at 4-hourly intervals as the number of injections increased from 8 to 20 to 50, and the duration of treatment from 32 hours to 8 days the total curative dose (C.D.<sub>50</sub>) fell from 80,000 to 1 600 to 360 units per kilo respectively. Similarly in rabbits injected twice daily merely doubling the number of injections from 8 to 16 and the duration of treatment from 4 days to 8 days, reduced the total curative dose (C.D.<sub>50</sub>) from 30,000 to 1,700 units per kilo. When the number of injections was kept constant and only the interval between them varied the curative dose (C.D.<sub>50</sub>) was similar whether injections were given every 4 hours twice daily or once daily (4 000, 1,770, and 4 000 units per kilo). On the other hand when the injections were given so frequently as to produce cumulative effects on the blood penicillin level, therapeutic efficacy was paradoxically reduced. Thus the curative doses of sodium penicillin given in 16 injections at 4-hourly, 2-hourly, and 1-hourly intervals were 4 000, 32,000, and 64 000 units per kilo respectively. When the total duration of treatment was fixed, and the number of injections varied the therapeutic efficacy of penicillin increased with the frequency of injection. In rabbits treated over a period of 4 days as the frequency of injection was changed from once daily to twice daily to every 4 hours and the number of injections correspondingly increased from 4 to 8 to 20 the total curative dose (C.D.<sub>50</sub>) fell from 50 000 to 20 000 to 1 600 units per kilo. Low concentrations acting over a long period of time were more effective than high concentrations over a short period. For an equal number of injections treatments given once daily were as effective as injections every 4 hours with a suggestion of an optimum interval of 8-12 hours.

With mapharside the drug is bound by the organism in competition with the tissues, and the single exposure to high concentration is as effective as repeated exposures to a lesser concentration. Penicillin, on the other hand, is effective only so long as it is present in the surrounding fluid, though it is apparent that the actual amount required to be present is very low. Thus, 50 4-hourly injections of only 7 units per kilo over 8.3 days were as effective as 8 4-hourly injections of 6,000 units over 1.3 days, similarly in animals treated twice daily, if the duration of treatment is reduced to 8 from 16 injections, the total curative dose ( $CD_{50}$ ) for injection is increased from 110 to 3,750 units per kilo. The spirochaetocidal effects of penicillin *in vitro* have been noted in concentrations as low as 0.01 unit per ccm. In rabbits treated by 50 4-hourly injections of 10 units per kilo a  $CD_{50}$  was obtained when penicillin was never demonstrable in the blood.

Methods of administration which yield blood levels above 0.01–0.2 unit per ccm waste a large part of the potential activity of the penicillin and treatment schedules should minimize wasteful peaks in the blood. This can be achieved either by repeated small doses at short intervals, continuous intravenous or intramuscular drip, or by using a penicillin in oil-beeswax delayed-absorption method though by the latter only the number of injections, and not the time duration of treatment, should be reduced. Milligramme for milligramme, penicillin in rabbit syphilis is between 10 and 20 times as effective as mapharside, though in the human subject it is apparently only 2 to 4 times as effective, and with both drugs rabbit syphilis is easier to cure than the human form. If it is desired to improve on results by increasing the dose of penicillin, then double the dose given over the same time is not likely to be nearly so effective as if double the dose were spread over double the time.

R R Willcox

**The Effect of the Sodium Salts of Crystalline Penicillin G, Crystalline Penicillin X, and Commercial Penicillins on Dark-field Positive Lesions of Syphilis.** OLANSKY, S., and PUTNAM, L. E. (1946) *J. vener. Dis. Inform.*, 27, 178

To date there is evidence that there are at least four penicillins in commercial penicillin. It has been shown that penicillin X is more effective than commercial penicillin in the treatment of gonorrhoea. Of 128 cases, 87.5% showed clinical cures after single injections of 25,000 units of penicillin X, as compared with only 64% of 68 cases with the same amount of commercial penicillin. The possibility therefore exists of a penicillin that is selective for the gonococcus and will not at the same time mask a concomitant infection with syphilis.

In this study the effectiveness of single doses of 50,000 units of two crystalline penicillins (G and X) was contrasted with that of several commercial penicillins as to the rate of disappearance of *Treponema pallidum* in patients suffering from

dark-field-positive primary syphilis. Of 10 patients treated with crystalline penicillin G, 6 had negative dark-field tests 8 hours after treatment, 2 at 10 hours, and 2 at 14 hours (average, 9.6 hours), 3 showed Herxheimer reactions and 2 had gonorrhoea which cleared promptly. Of 10 patients treated with crystalline penicillin X, only 2 were negative on dark-field testing at 14 hours, and 8 still had active treponemata in the lesions 24 hours after the injections. Both the successful cases showed Herxheimer reactions, and 6 also had gonorrhoea which cleared rapidly. Of 10 patients treated with a commercial penicillin G, 1 became negative at 12 hours, 4 at 14 hours, and 5 at 16 hours (average, 14.8 hours), 2 showed Herxheimer reactions. Of another group treated with commercial penicillin of predominantly G plus 16–18% X, 3 had negative tests at 16 hours, 4 at 18 hours, and 3 at 24 hours (average, 19.2 hours). There was one Herxheimer reaction in this series. Of 10 patients treated with a commercial penicillin containing 70% X, 7 were negative at 24 hours while 3 were still positive at that time. No Herxheimer reactions occurred in this group.

All patients showing Herxheimer reactions became dark-field-negative more quickly than others in each group. This may mean either that the Herxheimer is a manifestation of favourable response or that the associated fever was a contributory factor. It was thus noted that crystalline G was at least as effective as several commercial penicillins, and that X was less effective than G. There was no indication that any of the products so far tested might not mask a syphilitic infection.

R R Willcox

**The Therapeutic Effectiveness of Relatively Crude Commercial Penicillin in Early and Late Rabbit Syphilis.** FLEMING, W. L., and WOLF, M. H. (1946) *Amer. J. Syph.*, 30, 468

Experiments were undertaken to discover the minimum curative doses of penicillin in early and late rabbit syphilis. The same batch of penicillin was used throughout, it contained 293 units per mg, 115,000 units per ampoule, and 25% of factor X. The rabbits were divided into two groups, each of 50, and given varying dosages of penicillin 6 weeks (early) and 6 months (late) after infection. The total dosages were 500, 1,000, 2,000, 4,000, and 8,000 units per kilo given in equal fractions every 3 hours for 32 doses. Proof of cure consisted of surveillance for recurrent lesions, and lymph node transfers after 6 to 8 weeks and after 6 months. In early syphilis the  $CD_{50}$  (dose required to cure 50% of animals) was 1,100 units per kilo, and the  $CD_{99}$  over 2,000 units, in late syphilis the figures were 500 and over 2,000 units respectively. The amount of penicillin required to cure late rabbit syphilis was less than that required to cure early lesions. The experiment was complicated by the fact that 2 rabbits developed keratitis but gave negative lymph-node transfers, this does not affect the conclusions drawn.

T E Osmond

**The Rapid Treatment of Early Syphilis with the Combined Use of Penicillin and Mapharsen** BUNDESEN, H N, CRAIG R M SCHWEMLEIN, G X, BARTON, R L and BAUER, T J (1946) *Amer J Syph*, 30, 475

Twelve white and 36 coloured males and 12 white and 47 coloured females (107 patients) with lesions of syphilis positive on dark ground examination were treated by 60 intramuscular injections each of 5 000 units of penicillin, given every 3 hours (total 300 000 units), together with a daily intravenous injection of 40 mg of mapharsen (total 320 mg) and were observed for 18 months.

The average number of days required for reversal of serum reaction was 47.5 for primary, 95.0 for secondary, and 248.0 for relapsing cases. Thirty-four patients were considered treatment failures; these included 10 cases of relapsing secondary syphilis, 3 of primary lesions progressing to the secondary stage, 11 relapses as judged serologically, 7 resistant cases, 1 recurrence with neuro-syphilis, and 2 possible re-infections, details of which are given. Primary fever (presumably Herxheimer reactions) occurred in 76 patients and secondary fever in 59. The authors conclude that the amount of treatment given in this series is inadequate.

[This trial was carried out in the first 3 months of 1944; recent experience has shown that when 8 times as much penicillin and the same amount of mapharsen are employed, relapses still occur.]

T E Osmond

**Penicillin by Mouth in the Treatment of Late Cutaneous Syphilis** WALLACE E and PAUL, W D (1946) *Amer J Syph*, 30, 480

A woman, aged 52, had scattered, discrete, dull red nodules about 4 mm in diameter on the chin, and over the left scapular region there was an extensive lesion with gyrate outlines and a tendency to central clearing and peripheral spread, the border showing nodules similar to those on the chin. Biopsy revealed round cells, plasma cells and epithelioid cells about the blood vessels in the sub-papillary layer; the endothelium of the vessels was thickened and disorganized; the deeper infiltrate showed epithelioid cells and an occasional giant cell. Kolmer, Kahn and Kline tests of the blood were positive and the Kahn titre was 240 units. Cerebrospinal fluid tests were negative. The patient was given 7 800 000 units of penicillin over 10 days—that is 100 000 units combined with 2.5 g dihydroxyaminoacetate every 3 hours. The lesions showed continued regression 2 and 5 weeks after treatment. Illustrations show the lesions and biopsies before and after treatment.

[It would have been interesting to know the effect of this treatment on the blood reactions.]

T E Osmond

As a rule, owing to the prevalence of positive serological tests due to yaws, no case was diagnosed as early syphilis unless a positive dark field test could be obtained. Treponemata were absent from the lesions between 6 and 24 (average 14) hours after the onset of treatment and the average stay in hospital was 10 days. In contrast to Europeans, over 50% of whom experienced Herxheimer reactions, the incidence of such reactions in the African was negligible (0.09%), and all these were pyrexial responses in cases of secondary syphilis. No cases of urticaria were seen.

Clinical and serological relapse reinfections were under 0.6%, though the total number treated and the period of observation are not stated. Of 112 sero-positive dark-field positive cases, the percentages becoming sero-negative each month from 1 to 6 months were 18, 47.5, 56.25, 78, 87, and 98 respectively. Intercurrent infections, such as smallpox, relapsing fever, and other tropical diseases may produce a temporary elevation in the titre of the quantitative Kahn, which in some cases may be mistaken for a serological relapse.

R R Willcox

**Preliminary Results in Penicillin Treatment of Primary and Secondary Syphilis** (Premiers résultats du traitement de la syphilis primo-secondaire par la cure unique de pénicilline) VANSTEEN-ACKER, G (1946) *Reu. méd. Liege* 1, 207

**Penicillin Treatment of Syphilis** (La pénicilline dans le traitement de la syphilis; revue de travaux consacrés à cette question) BEESON, M B (1946) *Ann. Derm. Syph., Paris* 6, 395

**Toxic Effects of Penicillin Treatment in Pregnant Women** (In English) GARCIA-BIRD, J (1946) *Bol. Assoc. med. P. Rico*, 38, 220

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**Penicillin Therapy of Early Syphilis** STERN, F (1946) *Acta med. orient.* 5, 273

**The Treatment of Early Syphilis (in Africans) with Penicillin Sodium** COCHRANE, G C (1946) *E. Afr. med. J.*, 23, 287

The amount of penicillin administered was 2.4 mega units in 3 hourly injections over 7½ days.



## GONORRHOEA

**Oral Penicillin Treatment of Gonorrhœa** COHN, A, KORNBLITH, B A, and GRUNSTEIN, I (1946) *Amer J Syph*, 30, 485

The authors investigated the effect of penicillin given by mouth on gonorrhœa. Blood-serum levels after a single oral dose of 50,000 units varied from 0.03 to 0.25 unit per ml (average 0.08 per ml) after half an hour and from 0.015 to 0.125 (average 0.05 unit per ml) after an hour. When the single dose was 150,000 units the average levels were 0.52 and 0.029 unit respectively. Tests of cure included four lots of smears and cultures over a period of 3 weeks. For the experiment tablets containing calcium penicillin buffered with magnesium oxide and co-precipitated aluminium hydroxide and calcium carbonate were used. *Group I* 13 men and 5 women received 3 doses, each of 150,000 units, at 2-hourly intervals, 10 men and 3 women were cured and 3 men and 2 women were not. *Group II* 3 men and 11 women received 5 doses, each of 60,000 units, at 2-hourly intervals, 2 men and 8 women were cured. *Group III* 18 men and 11 women received 5 doses, each of 120,000 units, at 2-hourly intervals, 12 men and 9 women were cured. *Group IV* 40 men and 10 women received an initial dose of 150,000 units, followed by 50,000 units hourly for 6 doses and 150,000 units at the seventh hour, 36 men and all 10 women were cured. It appears that the time-dose ratio is important, hourly administration being necessary in order to obtain the best results, represented by a cure rate of about 90%. It is concluded that (1) by mouth about four times as much penicillin as is given in a single injection intramuscularly in water-in-oil emulsion is required to obtain cure, (2) the effect of oral penicillin may be minimized by irregular self-medication, which may lead to sensitization and resistance, and (3) oral penicillin may mask a concurrent syphilitic infection.

[In view of the fact that gonorrhœa is usually more difficult to cure in women than in men it is of interest to note that in *Group IV* all 10 women were cured, but only 36 out of 40 men. In the whole series the percentages of cures in men and women were almost equal.]

T E Osmond

**Penicillin for Gonorrhœa in the Female** MASCALL, W N (1946) *Lancet*, 2, 712

Attention is drawn to the dangers of false optimism created by publicity given to reports of the efficacy of penicillin in treating infection. The limitations of penicillin therapy for gonorrhœa are discussed in a detailed report of this form of treatment in 39 consecutive patients at the L C C (Whitechapel) Clinic. In 18 of the women penicillin failed to control the infection, and an additional 16 are regarded as probable failures. Women suffering from gonorrhœa alone were treated according to one of three schedules. (1) Five 2-hourly injections of 30,000 or of 60,000

units in aqueous solution, (2) a single injection of 200,000 units in aqueous solution, (3) a single injection of 150,000 or of 200,000 units in arachis oil and beeswax. There were 16 failures in this group of 24 cases. Gonococcal vulvo-vaginitis proved refractory to penicillin in the 3 children so treated. One of these cases relapsed after 150,000 and 300,000 units in divided doses had been given, and again after a single injection of 250,000 units in arachis oil and beeswax. Twelve patients also had syphilis, and were therefore treated with a total of 2,400,000 units—40,000 units 3-hourly by day and by night—and yet gonococci were subsequently found in 5 of them. The author suggests that the lack of success in gonorrhœa, even after a dosage as high as 2,400,000 units has been given, indicates the possibility that some strains of gonococci are naturally resistant or have acquired resistance.

V E Lloyd

**Penicillin Treatment of Acute Gonorrhœa and its Complications, and Early Syphilis (in Africans) as Practised in the East Africa Command.** COCHRANE, G C (1946) *E Afr med J*, 23, 285

Treatment of gonorrhœa with penicillin was introduced into the East African Command in February, 1945. The dose employed was 100,000 units of sodium penicillin given in 5 3-hourly injections of 20,000 units dissolved in 1 ccm of distilled water. Response was rapid, gonococci being absent from the smears within 3 hours in 50% and within 6 hours in 80% of cases. In spite of this the average stay in hospital was 4 days, at the end of which time if the urine was still hazy a specimen was examined to exclude bilharzial infection, and if the urethral discharge persisted a dark-field test was performed for *Trichomonas hominis*. Relapses were infrequent, and there were no failures or toxic effects. Good results were also reported with the complications of epididymitis, prostatitis, and gonococcal ophthalmia. Tests of cure, including a Kahn test, were done after 3 months, all tests were satisfactory in uncomplicated cases, but the number of such cases actually treated is not stated.

[Though mention is made of the possibility of a delayed or masked syphilitic infection, apparently no further blood tests were done after 3 months.]

R R Willcox

**Importance of the Gonococcal Strain in Resistance to Sulphonamides** (Sull'importanza del ceppo gonococcico nel fenomeno della sulfonamido-resistenza) MIDANA, A (1946) *Dermosifilografia*, 169

The author states that at least 90% of fresh cases of gonorrhœa are now sulphonamide-resistant, and suggests that naturally-resistant strains of gonococci, as opposed to strains with an acquired resistance, are partly responsible for present-day infections. He reports 6 cases of fresh infection

observed in 1943 when the proportion of resistant cases was relatively small. These were infected from the same source which itself presented a sulphonamide resistant infection. Three of the cases were infected in parallel and 3 in series, but in all the infection was sulphonamide resistant. In quoting work by Crosti on the passage of strains with an acquired resistance in man, the author implies that a naturally resistant strain caused the infection in the 6 cases reported, since in these cases the characteristic of sulphonamide resistance remained constant on transmission.  
H M Adam

**Masking of Early Syphilis by Penicillin Therapy in Gonorrhoea.** FROMER, S., CUTLER, J C., and LEVITAN S (1946) *J vener Dis Inform*, 27, 174

The possibility that the relatively small dose of penicillin employed in the treatment of gonorrhoea might mask a previously or simultaneously acquired syphilitic infection has always been borne in mind. It is already appreciated that fevers and chills are rare during the penicillin treatment of gonorrhoea and that when such reactions are experienced they are strongly suggestive of an additional infection with syphilis. Such a patient may develop a primary sore in the ordinary way, or this stage may be missed and one or more of the signs of secondary syphilis may appear in a usual or attenuated form. Perhaps a positive serological test may be the only sign, and the incubation period too, may be prolonged.

Of 1 000 patients suffering from early syphilis 66 had received penicillin treatment for gonorrhoea within the previous 4 months. Of these 18 had Herxheimer like reactions at the time the penicillin was administered. It is postulated that, as the incubation period of gonorrhoea may vary between 7 and 30 days and that of syphilis between 7 days and 4 months, combinations of long and short incubation periods of these two diseases may explain why some patients get febrile reactions and others do not. Thus if the syphilis is contracted before the gonorrhoea or if a long incubation period for gonorrhoea is combined with a short incubation period for syphilis, the patient would be highly parasitized and therefore liable to give a febrile reaction when the treponemata were killed by penicillin. On the other hand if the incubation period of the gonorrhoea is short and that of the syphilis long the patient being less highly parasitized, is less likely to show a Herxheimer reaction.

Three cases are quoted in support of this thesis. One patient showing a febrile reaction had a history indicating that the syphilis was contracted before the gonorrhoea while one with and one without a febrile reaction were assumed to have acquired the two diseases simultaneously. The one with the reaction developed a sore within a month and secondary signs within 2 months. The other developed no primary sore but secondary signs appeared after 4 months though as no serological tests were performed before this it is not known exactly at what period the blood

became positive. It is concluded that it is a safe precaution to subject all patients displaying a febrile reaction while under penicillin therapy for gonorrhoea to a clinical and serological scrutiny for 4 months after treatment.

[As mild fever may be missed in patients treated at home it would be safer to adopt this regimen for all cases of gonorrhoea treated with penicillin.]

R R Willcox

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**Penicillin Treatment of Gonorrhoea (Chemotherapie der Gonorrhoe mit Penicillin. Erfahrungen an einem grosseren Krankengut).** SCHUERMAN, H and BOHLER K H (1946) *Med Klinik*, 41, 283

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# SMEAR AND CULTURE DIAGNOSIS IN GONORRHŒA\*

BY

J W McLEOD

The subject of the diagnosis of gonorrhœa may be considered under three main headings apart from clinical diagnosis. The first is how far smear diagnosis is reliable and what are its limitations, the second is whether culture methods are superior to or at least adjuvant to direct microscopical observations and, if so, what the best methods may be, and the last to what extent reactions based on immunity supplement the above methods.

## Diagnosis from Direct Microscopical Examination of Smear Preparations

Everyone is familiar with the appearance of a typical smear from acute gonorrhœa containing numerous intra-leucocytic diplococci. In more chronic and subacute infections, however, there may be preparations in which the gonococci are not easily recognized, and this is particularly so in those from females, in whom other bacteria are often present, and in whom the numbers of gonococci tend to fluctuate. An American worker has recently stated that the superiority of culture over smear methods has been overstated. I cannot agree, and I want to make one or two points which force themselves on any bacteriologist who does much of this kind of work.

When there are only small numbers of gonococci in a preparation it becomes difficult to identify them with certainty, and there are two reasons for this. First, Gram-positive cocci present in small numbers will on occasions have been taken up by the phagocytes and will have lost their Gram-staining. It is difficult to differentiate between staphylococcal and other Gram-positive cocci which have lost their usual staining on the one hand, and scanty gonococci on the other. Secondly, there are undoubtedly a minority of Gram-

negative cocci which appear in the genital tract which are not gonococci, that is my experience, and also the experience of other observers, for example Reymann (1941, 1943) in Scandinavia. Such organisms appear in 1 to 2 per cent. of cases.

Table I shows the characteristics of six strains of *Neisseria* which were obviously not gonococci and which were obtained in a series of three hundred cases examined for gonorrhœa by culture. In one of these the colonies were quite numerous and this was a case in which there was a positive smear. Here it is possible that examination of the smear alone might have led to a wrong diagnosis. In four other cases there were only a few colonies of Gram-negative diplococci, but as the smear was negative a mistake was unlikely to have arisen. However, as long as such possibilities exist, even in a few cases, it would be difficult to appear in a Court of Justice and plead with conviction that a

TABLE I

GRAM-NEGATIVE DIPLOCOCCI, NOT GONOCOCCI, FOUND IN COURSE OF INVESTIGATION OF 300 CASES

Culture	Sugars	Agar	Smear
1 Opaque pigmented colonies ++	0	0	+
2 One colony convex and adherent	G+ M+ S-	0	-
3 Colonies ++ convex, opaque	G+ M+ S-	+	-
4 Colonies scanty, opaque, rather yellow	0	+	-
5 Colonies scanty	G- M- S-	0	+
6 Diplococci tend to grow in chains	G- M- S-	-+	-

0=no observation

\* An address to the Medical Society for the Study of Venereal Diseases, January 25, 1947.

typical preparation in which Gram-negative diplococci appeared necessarily showed the presence of gonorrhœa

### Methods of Culture

Table II shows smear and culture results in a series of 275 cases under the care of Dr Dorothy P Priestly, who was in charge of the female venereal disease clinic at Leeds. They were suspected cases of gonorrhœa, and, according to the combined smear and culture results, 50 per cent were positive. Smears were described as "typical" which showed numerous Gram-negative intracellular diplococci "Completely identified" under culture means that the organism was separated in pure culture, that the sugar fermentations were correct, and that inability to grow on agar was demonstrated. The remainder were identified on the grounds that typical colonies which gave a positive oxidase reaction were shown to be made up of Gram-negative diplococci.

TABLE II

SMEAR AND CULTURE RESULTS COMPARED  
(275 CASES)

Smear	Culture
29% positive (20% typical)	42% positive (29% completely identified)
Both C and U positive in 7%	Both C and U positive in 22%
Urethra positive in 24%	Urethra positive in 32%
Cervix positive in 16%	Cervix positive in 33%

50% of all cases positive by smear or culture

Table III demonstrates the possibility of improving the methods of culture for diagnosis. In 1927 we were simply doing culture on heated blood agar described as "chocolate". The numbers are too small to justify any firm conclusions, but the indication is of a rising percentage of positive results with improvement of the medium and the introduction and modification of the oxidase reaction. These earlier successes were followed up by recording the results in a big series of clinical cases. In a total of over 2,000 cases we obtained more than 100 per cent increase in the positive findings by adding the culture results to those obtained by smear examination.

### SOME THEORETICAL ASPECTS

Table IV shows the results of a number of experiments undertaken some years ago in

TABLE III

RESULTS OF CULTURES IN SUCCESSIVE PERIODS

Cases	Period	% Positive	Method
23	1927	17%	Chocolate
125	1927-28	31%	„ and dimethyl*
125	1928-29	50%	„ and tetramethyl*
25	Dec 1929	56%	Special medium and tetramethyl

\* Dimethyl etc., means the use of a solution of dimethyl *p*-phenylene diamine hydrochloride as an indicator of oxidase + colonies

order to see how the gonococcus survived in various fluids which were not quite sufficient to maintain life. It would seem that meat extract alone supports the gonococcus poorly, and that peptone, though helpful, is not tolerated well when concentrated. These results suggest that there may be substances in peptone which are actually lethal to the gonococcus, and Table V indicates that blood added to the medium may protect from such substances. With a small amount of peptone, growth occurred with the addition of 1 per cent of blood, but the initiation of growth became more difficult as the peptone was increased, until, with 5 per cent peptone, growth was abundant only where 5 per cent or more of blood was also present.

It was found that some amino-acids inhibited the growth of the gonococcus and others favoured it, as shown in Table VI. Partly as a result of that work, and partly as a result of experiment, we have finally adopted,

TABLE IV

SURVIVAL OF GONOCOCCUS IN VARIOUS FLUIDS  
INADEQUATE TO MAINTAIN GROWTH

Medium	Time of survival (in minutes)
Meat extract + 0.1% peptone	20
„ „ + 0.25% „	160
„ „ + 0.5% „	100
„ „ + 1.0% „	60
„ „ + 2.5% „	20
Water	25
Physiological saline	35
Ringer's solution	75

and for many years used the ordinary nutrient agar reinforced with blood, and as far as the gonococcus is concerned, heated blood (chocolate medium) seems to give better results than does unheated blood. There is also increased growth with an increased amount of blood, and for the gonococcus we use a medium of this kind and raise the blood concentration from the usual 5 or 10 per cent to about 20 per cent.

Table VII shows the contrasts between *p*-phenylene diamine and its various methyl substitution products in respect of their reactions with mild and strong oxidizing agents on the one hand, and bacteria on the other. These compounds become more susceptible to oxidation as more methyl groups are introduced. The original unsubstituted product is difficult to oxidize, with the monomethyl compound a yellow-brown colour results, with the dimethyl compound a maroon colour, and with the tetramethyl compound a violet colour. With a strong oxidizing agent a black pigment is finally obtained with the first three, and the bacterial action corresponds to that of the strong oxidizing agent. With the tetramethyl compound there is a deep violet colour only, which probably means that the blackening depends upon some polymerization which is blocked by full methyl substitution. That is the theory of this reaction, which is by no means confined to the gonococcus.

TABLE V

TO SHOW THAT PEPTONE INTERFERENCE WITH GROWTH IS ELIMINATED AS AMOUNT OF HEATED BLOOD IN THE MEDIUM IS INCREASED

Blood concentration	Growth of gonococcus					
	10%	5%	2%	1%	0.1%	0.2%
10%	++	++	++	++	++	++
5%	++	++	++	++	++	++
2%	++	++	++	++	+	+
1%	++	+	+	+	+	0
Concentrations of peptone added to meat extract						
	0.1%	0.2%	0.5%	1%	2%	5%

TABLE VI

EFFECT ON THE GROWTH OF THREE STRAINS OF GONOCOCCUS OF AMINO-ACIDS IN BROTH ENRICHED WITH 0.25% BLOOD AND HEATED AT 75° C

Amino-acid added	Strain 1	Strain 2	Strain 3
Glycine 0.5%	0	0	0
" 0.1%	55 colonies	++	0
Taurine 0.5%	++	++	25 colonies
" 0.1%	++	++	0
None—control	0	++	0
None—control	++	++	0

TABLE VII

Reagent	Effect of mild oxidants e.g., $H_2O_2$	Effect of strong oxidants, e.g., $K_2Cr_2O_7$	Effect of oxidase-active bacteria exposed to reagent and air
<i>p</i> -phenylene diamine hydrochloride $HCl \cdot H_2N \text{---} \text{C}_6\text{H}_4 \text{---} NH_2 \cdot HCl$	—	Formation of black pigment	Slow development of black colour
Monomethyl <i>p</i> -phenylene diamine hydrochloride $HCl \cdot CH_3HN \text{---} \text{C}_6\text{H}_4 \text{---} NH \cdot HCl$	Faint yellowish-brown	Formation of black pigment	Rapid development of black colour
Dimethyl <i>p</i> -phenylene diamine hydrochloride $HCl \cdot (CH_3)_2N \text{---} \text{C}_6\text{H}_4 \text{---} NH \cdot HCl$	Formation of maroon colour (Wurster's red)	Formation of black pigment	Slower development of black colour after preliminary maroon stage
Tetramethyl <i>p</i> -phenylene diamine hydrochloride $HCl \cdot (CH_3)_4N \text{---} \text{C}_6\text{H}_4 \text{---} N(CH_3)_2 \cdot HCl$	Formation of violet colour (Wurster's violet)	Formation of deep violet or purple colour	Development of deep purple colour after preliminary violet stage

TABLE VIII

THE MORE IMPORTANT OXIDASE POSITIVE AND  
NEGATIVE BACTERIA

Positive	Negative
<i>Neisseria</i> (strong)	Coliform group
Many vibrios (strong)	<i>Salmonellæ</i>
<i>Brucellæ</i> (moderate)	<i>Corynebacteriæ</i>
<i>Hæmophilus</i> (weak)	<i>Streptococci</i>
Anthrax and anthracoids	<i>Staphylococci</i>
(moderate)	
<i>B. Mallei</i> (moderate)	<i>Sarcinæ</i>
<i>B. Pyocyaneus</i> (moderate)	Anærobes

TABLE IX

FIGURES FOR SMEARS AND CULTURES FROM THE  
LEEDS BACTERIOLOGICAL LABORATORY

		Smears		Cultures	
		Number	%+	Number	%+
1938	male	944	19.8	660	2.0
	female	1,282	7.9	1,263	21.2
1944	male	1,302	17.0	448	4.25
	female	2,021	9.75	1,171	18.0
1946	male*	—	—	1,653	3.5
	female	5,530	4.0	5,642	10.0

\* No smears from males examined in Bacteriological  
Department

although there are many bacteria which are negative when tested in this way (see Table VIII). The great strength of the reaction is that no matter how a colony is overgrown it will show up. In this respect the results are superior to those obtained with media on which the pathogenic organism is colourless and the non-pathogenic is coloured, as on many media used for separating pathogenic coliforms from the faeces.

I do not want to claim for my colleagues and myself any originality in using the oxidase reaction, because it has been long under investigation by many observers. The earlier observations deal with questions like the oxidizing granules in the polymorphonuclear leucocytes and marrow cells, and its first use was mainly related to pathology. Christiansen and Becker (1938) claimed that the credit for introducing the oxidase reaction to bacteriology should go to Loele. Actually Loele drew attention to the possibilities of the oxidase reaction in a paper which appeared in 1928, the same

year as one by Gordon and myself, and he extended these observations in 1929. His work should not have been overlooked in our subsequent publications (Ellingworth and others, 1929; McLeod and others, 1934). I note, however, from Loele's paper, that Wurster drew attention to the oxidation of tetra-methyl *p*-phenylene diamine by yeast the year before I was born! Nevertheless the method does not appear to have been seriously used in the cultural diagnosis of gonorrhœa in Germany. No general practical application was in fact made until 1934, when we (McLeod and others) published a paper on the subject of its use in the diagnosis of gonorrhœa. From that time it was extensively explored in America (Leahy and Carpenter, 1936; Thompson, 1937), and I am convinced that if those who have the responsibility of making bacteriological investigations for the detection of carriers of cholera were to use it, it would yield valuable results. There is no opportunity, however, of making practical demonstrations of that kind in this country, and I do not know that anyone has taken it up in countries where cholera is endemic.

In practice the oxidase method is most simply used by pouring a weak solution of tetra-methyl *p*-phenylene diamine hydrochloride over the plate and letting it run off, soaking away the excess with a piece of sterile blotting paper, and as soon as the colonies begin to dry picking off purple colonies of characteristic appearance. Although this reagent oxidizes spontaneously in air, it only develops a light violet colour, which deepens markedly in contact with the gonococcal colonies. The dimethyl compound, although also useful, has the disadvantage that the red pigmentation goes over to black and that at some stage in the production of the black colour there is a marked bactericidal effect.

#### Effect of Gaseous Environment on Growth of *Gonococcus*

In view of the action of gaseous environment on bacteria, and especially the influence of carbon dioxide on *Brucella Abortus*, the effect of gaseous environment was studied. On trying out the gonococcus in an atmosphere with increased CO<sub>2</sub> content, we got the impression that the results were better with some strains. This has been confirmed by both Danish and American observers (Reymann, 1941; Thompson, 1937), and our practice is to give cultures a preliminary incubation in a jar which has been flushed from a cylinder containing compressed air with 8 per cent carbon dioxide.

## Recent Results

Reymann published (in Danish 1941, and in English 1943) an extensive thesis on this subject. He found that by the methods described above (with slight modification) he was able to get better results than with the German methods which have been largely used and most often recommended (Neumann, 1938).

For the purpose of checking the value of these methods after they had been in routine use for a number of years and were not receiving quite the same close attention as in the initial period of trial and establishment, I took the figures from the books of the Leeds bacteriological laboratory for three representative years. The year 1938 represents a pre-war year, and 1944 a war year, during which the late Dr Bibby was in charge of the Leeds Venereal Disease Clinic. The year 1946 is from the post-war period when Dr Lees was in charge.

The male smear and culture results do not cover the same cases. Smear examinations were used both for diagnosis and to check cure after treatment—cultures only for the latter. The female smear and culture results cover the same group of cases, and in them examinations for diagnosis were more frequent. Under the control of Dr Lees and Dr Walker the total number of examinations of female cases has been considerably greater and the percentage of positive reactions has fallen (Table IX). There has been more than 100 per cent increase over smear results in positive culture examinations in females during these years.

TABLE X  
GONOCOCCAL COMPLEMENT FIXATION TEST

	1937-44	1945-46
Total	388	2,540
Negative	38%	64%
Doubtful	28%	25%
+	18%	7%
++	16%	4%

## Results Obtained with the Gonococcal Complement Fixation Test

In the first instance various methods were tried, including the use of both commercial antigens and those which we prepared ourselves by Price's method (1932 and 1933). It was however with a freshly prepared and standardized antigen from 18- to 24-hour cultures made up for each day's work (as recommended by Tulloch, 1923, 1924, 1925) that we obtained results which were to us most convincing. The data over a period of 10 years are given in Table X. From 1937-44 a much smaller number of examinations was done,

mostly related to such conditions as suspected gonorrhoeal arthritis or salpingitis. In the second period the test was used much more extensively, and as was to be expected the number of positives was considerably lower.

## Transport of Material for Culture

There are many practical difficulties which arise in using cultures for this purpose, the most obvious being the rapid transport of material to the laboratory. Results of culture when swabs are sent from a hospital are very different from those obtained from cultures made in venereal disease departments where there are incubators and jars for keeping cultures in air and CO<sub>2</sub> till they are sent to the laboratory. There have been many suggestions for obtaining the secretions and conveying them to the laboratory in good condition. The more popular in the United States have been methods of freezing (Wortman and others, 1941, Sanderson and Allison 1942). The swab, which before use is treated with 15 per cent glycerine, is put in a tube and the tube immersed in alcohol to which carbon dioxide ice has been added. It is then transferred to a thermos flask to which are added a few lumps of dry ice. Another method recommended is the portable incubator (Harrison, 1937). Both methods have given valuable results, but they are elaborate and include the transmission of heavy apparatus, and dry ice is not in all circumstances easily obtained.

The simplest and most interesting method seems to be one recently described by Stuart (1946), who points out one or two apparently significant theoretical aspects of the subject. For example the death of the gonococcus by drying is caused by increased rapidity of oxidation if the gonococci can be kept under conditions of reduction this does not take place. The method which Stuart has finally adopted is to use small screw-capped bottles filled with 0.3 per cent. agar, which gives the most suitable physical conditions, the agar contains one part in 1,000 of thioglycolic acid neutralized with NaOH and the whole is buffered with 1 per cent. glycerophosphate and 1 part in 10,000 calcium chloride. One part per 500,000 methylene blue is added in order to check the persistence of conditions of reduction. As long as these are satisfactory the agar remains colourless. The swab is



pushed into the bottle, its stem is cut off flush with the rim, and the cap is screwed down. Stuart gives figures showing that by the use of these methods the gonococcus will remain capable of sub-culture up to two, three, or four days, and there is no tendency for the other organisms to grow out—they are at least as much restrained as the gonococcus.

The results of culture and gonococcal complement fixation tests during this period depended mainly on the work of my colleagues Miss Bertha Wheatley and Messrs K. I. Johnstone, K. Zinnemann, and D. Dolby, to whom I wish to express my indebtedness.

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## DISCUSSION ON THE PRECEDING PAPER

DR G. L. M. McELLIGOTT (the President) was in favour of cultures as against smears. He had been brought up to the idea that the gonococcus hated the cold, and to know that it could be frozen with impunity was reassuring. He asked what Prof. McLeod thought of portable incubators for use in country clinics where the choice of the best method of transporting the gonococcus from clinic to laboratory was important. Dr. Stuart's work sounded extremely interesting. To a question about how long one kept the gonococcus in the semi-fluid agar, Prof. McLeod replied that it was a matter of preservation—it was kept there until it could be cultivated.

DR T. E. OSMOND said he had always taught that the gonococcus did not mind the cold, in fact when he had it growing rapidly if he could not sub-culture for a few days he put it in the ice chest during the interval. Prof. McLeod replied that the question of cold might not be so familiar to clinicians as to bacteriologists. Oddly enough the accepted method to-day of preserving all bacteria was to dry them from the frozen state. Dr. Osmond asked whether Prof. McLeod had adopted the method for identifying the gonococcus recommended by Thomson, that is, solubility in weak alkali. In his experience the gonococcus colonies were much more clearly visible on a colourless medium—where one could see the details, the shape, the scalloped edge, and the striations—than on a blood medium. He had used the medium described by Thomson, which contained the usual ingredients plus hydrocele

fluid, and also the chocolate medium agar, though the gonococcus might grow as well on the latter, it was much more difficult to see the nature of the colonies. Prof. McLeod said he had not tried Thomson's test. The best colour contrast was largely a question of what one was accustomed to. A chocolate background was quite useful, but he noticed that Reymann on going into this in detail had chosen a chocolate medium reinforced with ascitic fluid. He preferred Dr. Osmond's suggestion of hydrocele fluid. Noguchi, in cultivation of spirochaetes, had great difficulty because of the varying qualities of different samples of fluid, and that would probably apply also to the gonococcus. Dr. Osmond asked whether Prof. McLeod considered hæmoglobin an essential or an advantage, and Prof. McLeod replied that the blood pigment appeared to be an important part of the blood in this connexion.

DR LEES said that formerly he had been sceptical of the superiority of cultures over smears in diagnosing gonorrhœa, but since using the excellent service provided in Leeds he had become convinced that many cases of chronic and latent gonorrhœa, especially in females, could be detected only by efficient cultural examination. It had been a source of surprise and disappointment that so few Army and civilian laboratories could grow gonococci, even in cases where direct smears from the case showed the organisms to be abundant. His former colleague, Dr. Betty Walker, had recently examined a series of 140 consecutive cases in which a diagnosis of gonorrhœa had been made,

and in 138 of these patients positive cultures had been obtained. The remaining two had negative cultures, but Gram negative diplococci were found in smears, and the patients' consorts suffered from gonorrhoea. The failure of the cultures in these cases might be due to errors of technique, but in this series there were 85 cases with negative smears and positive cultures.

The technique of collection of the specimen was important and should avoid contamination as much as possible. He preferred to use a platinum loop rather than a dressed probe, and a plate should be used rather than a sloped tube or bottle as it facilitated examination and picking off colonies. The freshness of the medium was important, and he collected the culture plates as far as possible on the day they were to be used, and stored them in cool conditions. They were placed in the incubator at once after inoculation and, if not to be sent to the laboratory within 2 hours, they were placed in a special container and gassed with the mixture of 8 per cent. CO<sub>2</sub> and air. It was helpful to place damp cotton wool in the incubator and container so that the plates did not dry readily, and also to have the temperature of the incubator checked regularly by a responsible person, otherwise the temperature might fluctuate widely, and any rise above 37° F was associated with indifferent diagnostic results. He usually used one plate per patient, one half being inoculated with urethral secretion, and the other half with either prostatic or cervical secretion.

He employed cultures as a routine for the diagnosis and tests of cure in females, tests being made once per week for 4 weeks after treatment, and afterwards during the last day of three successive menstrual periods, or once a month for 3 months if the patient was not menstruating. In male cases he relied on smear diagnosis in early acute cases unless there were some medico-legal indications for more complete identification of the organism. But tests of cure in the male required cultural technique just as much as tests in the female, and he usually made tests of the urethral and prostatic fluid once a month for 3 months after treatment, and at any intermediate time if the clinical signs indicated a relapse.

Prof McLeod, he thought, had dealt very little with organisms such as might be called pseudo-gonococci, or with the occurrence of meningococci. These organisms presented difficulties in some cases of ophthalmia or vulvovaginitis of children. He recalled one case where Major Hughes had isolated and fully identified meningococci in a case of ophthalmia in a young soldier. This soldier was stationed at a very isolated site, and infection with gonorrhoea was considered highly improbable.

While he was convinced of the value of cultures in diagnosis of gonorrhoea, a series of negative results was possible in certain cases of chronic infection with a focus of infection shut off from the surface. In such cases the gonococcus complement fixation test was of value. These cases were usually suffering from metastatic lesions such as iritis or arthritis, and the focus of infection was in a fibrosed seminal vesicle or Fallopian tube.

He asked for advice on the viability of the gonococcus in urine, and whether such specimens were worth sending to the laboratory for diagnosis of gonorrhoea.

To this Prof McLeod replied that his own experience of examination of urine had been very disappointing. It was usually a long time in coming to the laboratory. He had noticed that the Americans, who were enthusiastic about freezing methods, recorded many results where the urine was frozen, they spun it down immediately, and then froze the sediment and sent it for examination. This method appeared to have worked almost as well as immediate culture.

DR. I. N. ORPWOOD PRICE thought it could be said in general terms that the results obtained from smears and cultures depended upon the stage of the disease at which these specimens were taken. Thus in the acute stages of gonorrhoea an equal number of positive results would be obtained by either method. In the later stages of the disease and in treated cases, culture methods gave better results. At the same time it should be more clearly realized that culture methods depended on two factors, the quality of the medium, and the method of inoculation. Apart from its essential growing qualities, three things were necessary in a medium: (1) a firm surface, (2) that the pH should not be below 7.3 or above 7.6, and (3) a moist atmosphere. Even when inocula were made from early acute cases the results obtained by different operators varied enormously. The most potent cause of failure was the omission of the preliminary cleansing by spirit of the external mucous membrane from the surface of which the inocula were made.

The production of gonococcal antigen for use in the complement fixation test depended on the type of medium used to grow the organism, and Dr Price recommended the use of egg-albumen agar.

MR. A. J. KING felt that Prof McLeod did less than justice to those working in venereal disease control when he said that there was a delay of six years before the oxidase test was applied to the identification of gonococcal cultures. Dr Price published his work on the subject in 1929 and the test was in routine use at the Whitechapel Clinic from 1930 onwards. Prof McLeod replied that he was thinking of the wider use, there was a gap of six or seven years outside this country.

Mr King then asked whether Prof McLeod would be prepared to swear in a Court of Law that he had grown gonococci in culture if he were unable to apply sugar fermentation tests in sub-culture. In fact, would he accept as the gonococcus an organism which grew like the gonococcus, which looked like that organism, and which gave a positive oxidase reaction? To this Prof McLeod replied that if he knew he was going into a Court of Law he would not stop short of isolating the organism in pure culture and determining its sugar fermentations, but for everyday diagnosis the appearance of the colony, which was very characteristic, and the facts that

it gave a sharp oxidase reaction and that it was morphologically a frank diplococcus, were quite adequate for the purpose of diagnosis. A percentage of strains was always examined for sugar fermentations just to make sure that no errors were being made.

Asked what were his experience and views on the substitution of acetone for alcohol in the modified Gram stain, Prof McLeod replied that he could make no comparison as he always decolorized with aniline-xytol.

DR HEYWOOD. In September last, while in Copenhagen on holiday, Dr Heywood had met Dr Reymann, who showed him the diagnostic and therapeutic routine used in Danish venereal disease clinics. The diagnosis of gonorrhœa by cultural methods interested him clinically, and he had gone to some pains to find out how the Danes carried out this procedure. The two clinics he visited took specimens on dressed probes, and these were placed in an ordinary test tube containing about 10 cm of turbid fluid. He had asked what it was, but owing to the language difficulty was not able to understand the reply fully. He thought it must be something like the medium Dr Stuart was using in Glasgow. The specimen in the test tube was sent by post to the State Serum Institute, which carried out the cultural diagnosis of gonococci for the whole of Denmark. Dr Reymann had for a number of years been in charge of the cultural work at the State Serum Institute, but he had recently relinquished it to Dr Alice Reyn. The specimens on arrival were plated in aluminium Petri dishes, which he had not seen before, and he wondered whether they were obtainable here, because they would have a longer life. The dishes contained Reymann's modification of Prof McLeod's medium. They were incubated in tall glass jars in which carbon dioxide was generated from a mixture of sodium carbonate and sulphuric acid, and at the end of 16 to 24 hours they were subjected to the oxidase test and the positive colonies were Gram-stained, fermented, and sub-cultured. This answered one of Mr King's questions as to what would be sworn to in a Court of Law. In Denmark the sub-culture was grown at 22° C to eliminate the confusion of the gonococcus with the micrococcus catarrhalis. The primary culture was continued for a further day in ordinary atmospheric conditions because, according to Dr Reyn, the carbon dioxide culture for 24 hours gave only 80 per cent of possible positive results, and the further 24 hours' incubation gave better results.

Prof McLeod was interested to hear what Dr Heywood had said about Dr Reymann's work. He was in Copenhagen at an earlier period and knew the laboratory and the general line of work. They had used the aluminium plates for many years, particularly in the diagnosis of whooping cough, but his experience of aluminium plates was disappointing, the metal corroded, but it might be a question of getting a suitable preparation of aluminium.

DR W NEVILLE MASCALL said that although he was a clinician he had always been interested in

this subject and about 1934 published a paper dealing with the pathological diagnosis of female gonorrhœa, in it he tried to point out that a large number of cases would not have been diagnosed correctly if cultures had been omitted. Since then he had been an advocate of culture methods, but he would like to see a greater use of plates instead of slopes. While working at the Whitechapel Clinic a plate was inoculated from the posterior fornix of the vagina as a routine, and it was amazing how often that plate proved to be positive even when the other cultures were negative. He felt that most probably it was due to the fact that the greater surface area allowed the gonococcus to breathe more freely. The gonococcus did not like to work with a lot of other organisms present, and part of the difficulty of diagnosis in females was undoubtedly due to the fact that there was always a heavy secondary infection. He felt that if plates were used they would get even better results with the cultures than they did at present.

Recently he wrote a paper and was criticized for his method of Gram-staining because he used acetone in place of alcohol for decolorization. He was told that his diagnosis would not be so accurate as with alcohol. In view of this he had been doing a series of parallel stainings, using alcohol and acetone, and so far there was no appreciable difference between the two.

In the future planning of a medical service a central venereal disease laboratory should be established where specimens from doubtful cases could be sent for verification.

DR LAIRD did his own cultures and the results were reasonably encouraging. He was able to consider the different aspects of the case, the clinical side, the smear side, and finally the cultures, and in that way he believed that in a good proportion of cases a fairly accurate diagnosis could be reached.

The question of conjunctivitis due to the meningococcus rather than the gonococcus was a problem which he came across very early in the war. In conjunction with an eye specialist he published in the *Journal of the Royal Army Medical Corps* in about 1940 an account of two such cases. This possibility should be kept in mind in cases in which there was no other evidence of gonococcal infection.

DR MCELLIGOTT said that meningococcal conjunctivitis could not be such a rarity, because he had seen the condition in a medical student. This student had been examining a case of secondary syphilis when the patient coughed into his face and some saliva fell on to the student's conjunctiva. The eye was disinfected within an hour or two, but nevertheless conjunctivitis developed 10 or 12 days later. The original patient later came to the speaker's clinic, where the diagnosis of secondary syphilis was confirmed. Gram-negative diplococci were grown in culture from the syphilitic patient's throat and from the student's conjunctiva, the organism was found to be the meningococcus.

# LOGICAL WASSERMANN "PROBLEM" CASES\*

BY

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The syphilis Wassermann "Problem" cases is caused not only to the serologist but to the physician or clinician, upon whom devolves the responsibility for diagnosis. In the past there has been too little critical judgment by clinicians in assessing the results of the Wassermann reaction, and many practitioners may still regard a positive Wassermann reaction as in itself a diagnosis of syphilis.

In recent years there has been an enormous increase in the practice of serum testing for syphilis. In general hospitals a routine Wassermann test is now carried out on all donors, and often on recipients for blood transfusion. A blood test is now frequently asked for before marriage. At all big venereal disease clinics and ante-natal clinics a routine blood test is done on every case. It is therefore of great importance to the clinician to realize the limitations of tests for syphilis, for it is now known that these serum tests may give occasional false positive results, and there is no doubt that in consequence a certain number of patients in the past have been subjected to anti-syphilitic treatment on account of a positive Wassermann report which further investigation would have proved false.

In approaching this subject it is not my intention to delve into an abstruse scientific discussion regarding the biological causes for false positive Wassermann reactions but rather in a practical manner to mention the views held and to emphasize the limitations and pitfalls as a whole, and to stimulate discussion on the interpretations that should be placed on a positive Wassermann reaction which is not supported by the clinical data. In 1943 in this *Journal* Harrison and Osmond

called attention to the limitations of serum tests for syphilis. These authors particularly discuss the causes, prevention, and detection of false positive reactions and the prevention of a false diagnosis of syphilis when a positive Wassermann reaction is not supported by the clinical evidence. This contribution at the time was badly needed in order to emphasize the limitations of the Wassermann test.

False positives are generally classified as either technical or biological.

## Technical Causes

Since the discovery of the Wassermann test by Wassermann, Neisser, and Bruck in 1906, many variations in the technique have been devised by different workers, and consequently indifferent results are often obtained. In this country we are fortunate in having a standard Wassermann technique, and credit must be given to Colonel Harrison for his work on standardization. The No. 1, or Harrison, method reported in the Medical Research Committee Special Report Series No. 14 in 1918, and later described in detail by the late Dr. Wyler (1929) in the Medical Research Council's Report Series No. 129 and now commonly known as the Harrison-Wyler method, has been subjected to very thorough comparison tests against other methods, not only in this country but abroad, and its reliability has been conclusively proved. When it is competently carried out and the details followed and carefully standardized reagents used, it is one of the most reliable pathological tests we have.

The Medical Research Committee (1918) on the Standardization of Pathological Methods stated: "In the opinion of the Committee there is no process of bio-chemical diagnosis

\*An address to the Medical Society for the Study of Venereal Diseases on February 22, 1947.

that gives more trustworthy information or is liable to a smaller margin of error than the Wassermann test when it is performed with completeness and with proper skill and care" Harrison and Osmond (1943) say "This statement is probably as true to-day as it was when written a quarter of a century ago, but it is equally true that no group of tests has given rise through unskilful performance and through inadequate appreciation of their limitations to more unhappiness than have the serum tests for syphilis"

The performance of the Wassermann test requires skill and concentration. Any slackness may give rise to some technical error. Suppose, for example, there is a batch of seventy blood sera to be tested. This entails the drawing off in pipettes of sera from each numbered tube into another series of numbered tubes for one in five dilution with saline for the purpose of inactivation at 55° C. After inactivation, each diluted serum has to be placed in further correspondingly numbered tubes for the actual test. All this requires patience and care, otherwise a mistake may easily be made. Many anomalous results may have been reported in the past by unskilled technicians, not because the Wassermann test was at fault, but because the operator was at fault. In a well-run laboratory, and when a competent technician is performing the test, a mistake is seldom made.

Recently a patient was sent to the Endell Street Venereal Disease Clinic because his serum had been tested by a laboratory and reported as giving a double-plus Wassermann reaction. At the Endell Street Clinic the Wassermann and Kahn tests were twice found negative. At the same time a careful clinical examination revealed no history or clinical evidence of syphilis. As a further check the Tests were once more repeated, this time at two separate clinics, and the reports from both were negative. It was agreed that the first reported (+ +) Wassermann must have been a technical error and that the patient was not suffering from syphilis.

To prevent such mistakes, whenever a positive or doubtful result is reported which is not supported by clinical findings, a further specimen should be sent for verification. The Kahn test is also useful as a check on the Wassermann. In this way the risk of making a technical error is diminished. If the pathologist feels that there is still doubt in the mind of the clinician, he should have no hesitation

in asking for a blood specimen to be split and sent to another laboratory for comparison and verification.

There is also the possibility of a technical error in numbering or labelling specimens. Or occasionally a blood specimen is badly hæmolized, so that on inactivation at 55° C it becomes a solid chocolate-like mass. Such a serum is, of course, unsatisfactory for testing, and if such instances occur the method of taking blood specimens at the clinic should be overhauled. Another possible source of error (mentioned by Orsós, 1936) is an admixture of salvarsan (commonly from using the syringe with which an injection has just been made). Such a contamination even in high dilution readily leads to false positive results. Therefore separate syringes should be kept for taking specimens and not used for anything else. A further frequent technical mistake is bacterial contamination of a specimen. Sterile tubes and sterile syringes should be used, and the specimen, especially in hot weather, kept in the refrigerator.

#### Lability of Biological False Positive Reactions

There is now almost conclusive evidence to indicate that in some apparently normal individuals there may be a peculiar lability of the blood serum, either permanently or under the influence of some intercurrent disease, which may cause it to give a false positive reaction to Wassermann and other syphilis tests. This peculiar lability has been known for some time, and there is now an accumulating literature on the occurrence of such false positive reactions in certain diseases. It has been long known that animal sera, particularly rabbits, can give positive Wassermann reactions and flocculation tests.

Albrecht (1942) observed that normal rabbits gave 1.21 per cent positive reactions with the Chediak dried-blood modification of the Meinicke test. He further observed that the reactions given by such rabbits were uninfluenced by heat or cold, overfeeding or starvation, or by any intercurrent infection such as catarrh or gastritis.

Sachs (1942) published a paper on some aspects of the serology of syphilis, and discussed the question whether antibodies alone are responsible for complement fixation and

flocculation following the interaction between serum and tissue extracts. He states that although opinions in this respect may differ, it is unquestionable that another mechanism of serological reactivity exists, apart from that caused by antibody action.

According to Sachs. The reagents (tissue extracts, etc.) used for the serological syphilis tests are able also to react with the proteins of labile sera. The results of such an interaction are just the same as in true antibody reactions, complement fixation, or flocculation. The difference is due only to the fact that in these circumstances the extract components react immediately with the serum globulins while the specific reaction between antibody and antigen (or hapten) is secondarily followed by the same alterations inducing complement fixation or flocculation. This consideration makes non-specific reactions in the sero-diagnosis of syphilis understandable. It must be realized that the extracts used as antigens are not at all pure reagents. The specific component responsible for the antibody reaction is only a small share (chemically not sufficiently recognizable) which adheres to a big portion of ballast material originating from the tissues. This ballast material and its colloidal structure is of great importance because it may act like antigens—so to speak as 'pseudo-antigens'—but only because of its colloidal behaviour. The result is a non specific reaction which will occur the more easily the more labile the serum globulins.

Another explanation put forward assumes that non-specific reactions may be caused by antibodies related to those developing in syphilis or caused by symptomless infections. Sachs states that, although antibodies identical with those characteristic of syphilis may be produced in some other infectious diseases such as yaws, malaria, leprosy, and subacute bacterial endocarditis, he does not believe in the theory which endeavours to explain non-specific reactions in general by the same mechanism as that responsible for the Wassermann reaction.

Sachs points out 'that non specific reactions are more frequent and stronger when unheated serum is used instead of heated serum. Heating the serum, first recommended for the intensification of the Wassermann reaction on account of the destruction of the complement activity just weakens the reactivity and increases at the same time the specificity. An unheated serum of a pregnant non-syphilitic woman, e.g., may give a stronger complement fixation than a heated syphilitic serum, while the reactivity disappears completely after heating. On this account heating

the sera at 55° C for half an hour is one of the most important measures to warrant the reliability of nearly all serological syphilis tests. In flocculation tests, moreover, the sensitivity is increased in such a way. Only when a more concentrated sodium chloride solution is used as medium, as in Meinicke's clarification test, may unheated serum be used. The higher salt concentration prevents the reactivity of labile globulins and acts, therefore, in the same manner as heating which causes their stabilization.

Sachs therefore claims that it may be justifiable to assume a general biological mechanism for the lability reactions. Actually it is possible to obtain with nearly all sera a positive Wassermann reaction either if the sera are unheated or if the salt concentration is diminished. Both are understandable—the unheated serum yielding a sufficient lability and the diminution of the salt content facilitating the reactivity of the labile serum globulins. Sachs, in certain experiments with Dr Havelock Nelson, observed that 'in certain circumstances on using hypersensitive extract dilutions flocculation may be obtained with all sera at room temperature but that after a subsequent stay in the incubator only flocculations produced by syphilitic serum remain while the others dissolve. This shows that a degree of non-specific reactivity may be present in every serum.'

Thus, we may assume that in the Wassermann test there are two types of reactivity possible, viz. (1) antibody reactions (syphilitic type) (2) lability reactions (general biological type) responsible for false positive reactions.

Sachs states that complement fixation and flocculation are the consequence of the same alteration of globulins which may be caused either specifically and indirectly by antibody action or non-specifically and directly by serum lability. Although the flocculation tests are usually more sensitive than the Wassermann reaction, occasionally the opposite result may be obtained. The reason for this is that complement fixation occurs best when the antigen antibody complexes are in the stage of development and sometimes because of the dependence on optimum proportions just in the circumstances that do not induce a visible flocculation. On the other hand complement fixation may be inhibited by the non-specific components of the serum. Such an influence may cause a negative Wassermann reaction while flocculation is positive although complement fixation is more sensitive in principle. Moreover,

under suitable conditions, the Wassermann reaction is most specific. Because of these peculiarities, both complement fixation and flocculation must be used if the true evaluation of a suspected syphilitic serum is desired."

Kahn (1942, 1943) made a special study of the differential characteristics of non-specific and specific serological reactions. He observed that a non-specific reaction is weakened at 37° C and strengthened at 0° C, conversely specific reactions are strengthened at 37° C and weakened at 0° C. He also found that tissue extract antigens of excessive sensitivity can be prepared which will give about 40 per cent positive serological reactions in non-syphilitic persons. If the tests with excessively sensitive antigens are performed at cold temperatures the non-specific sensitivity can be raised to about 80 per cent. If the tests with excessively sensitive antigens are performed at cold temperatures with unheated sera instead of with sera heated for 30 minutes at 56° C, the non-specific sensitivity reaches about 98 per cent. Certain lower animals give 100 per cent of positive reactions when the tests are performed under the same conditions.

The above findings suggest that there exists what Kahn calls a "universal" serological (non-syphilitic reaction) given by human beings and animals, but that it is best observed under conditions of low temperature.

A further interesting observation made by Kahn is the possibility of biological false positive reaction in the presence of syphilis, e.g. a certain person has a tendency to give false positives, let us say during a cold. In due time he becomes infected with syphilis and begins to show specific positive reactions. Then, when he contracts a cold, he is likely to give at the same time both specific and non-specific reactions. Should he later become specifically serum-negative following therapy, he will give the non-specific reaction only when he has a cold. Similarly, certain neuro-syphilitic patients treated with malaria give positive specific serological reactions before malaria therapy, both specific and non-specific reactions soon after malaria, and in due time only specific serological reactions.

Kahn has, in consequence, developed a new Kahn verification test which can be applied to those difficult "problem" cases when a positive Wassermann reaction is reported in the absence of clinical evidence of syphilis.

If the Kahn verification test indicates in such a case a non-luetic type of reaction, one might be justified in assuming a biological false reaction and that the case is probably non-syphilitic.

#### Diseases in which Pseudo-positive Wassermann Reactions have been Recorded

The following are diseases in which pseudo-positive reactions have been recorded

yaws  
malaria  
trypanosomiasis  
kala-azar  
African tick fever  
pellagra  
beri-beri  
relapsing fever  
rat-bite fever  
leprosy  
typhus fever  
hepatic distomiasis  
tropical ulcer  
chronic diseases of liver  
scarlet fever  
measles  
diabetes mellitus  
tuberculosis  
lupus erythematosus  
malignant tumours  
sclerodermia  
glandular fever  
(infective mononucleosis)  
German measles  
atypical pneumonia and transient  
bronchopneumonia  
Vincent's angina  
various subacute inflammations of  
unknown origin  
staphylococcal septicaemia  
eclampsia  
lymphatic leukaemia

This list of diseases is formidable. The literature on the serological tests for syphilis is enormous—Eagle (1937) in his book on the laboratory diagnosis of syphilis gives over 1,000 references alone. I shall, therefore, confine my remarks to a few outstanding features that may be of interest.

In yaws a positive Wassermann reaction occurs after three or four weeks in over 80 per cent of active cases. Butler (1936) insists that yaws is syphilis modified by race, climate, immunity, extragenital infection in childhood, and absence of specific immunity. Davis (1944) reviews the findings of the American Committee on Medical Research of the Office of Scientific Research and Development. According to their findings false positive

serological tests are common (more than 10 per cent. of cases) in leprosy, malaria in the acute stages, infectious mononucleosis, vaccination against smallpox, rat-bite fever due to spirillum minus, relapsing fever, lupus erythematosus, and possibly certain types of atypical pneumonia. They state that there is no reliable evidence that the serological tests are significantly affected by pregnancy, menstruation, scarlet fever, jaundice (other than infectious), subacute bacterial endocarditis, tuberculosis, or hypoproteinæmia, and that there is inadequate data available regarding the incidence in measles, mumps, infectious hepatitis, lymphopathia venereum, chancroid, and many other diseases. It is mentioned that transient false positive reactions may occur in apparently normal persons without recent illness. Even persistently positive reactions may occur in non syphilitic patients. Since a large proportion of sero-positive patients have no syphilitic lesions at necropsy, it is entirely possible that many sero-positive persons without a history or signs of the disease have been mistakenly diagnosed and treated for latent syphilis. The incidence of transient false positive tests following acute infections depends largely on the frequency of testing during the acute and convalescent stages. Although post-infectious or post-vaccinal positive reactions occasionally last as long as three months, most become negative within a few days or weeks. The Committee state that, since it is customary to perform serological tests on hospital patients only on admission, at which time acute infections have not fully developed their antibodies, it is likely that the ability of many common infections to lead to false positive serological tests is grossly underestimated.

Gell (1931), after a bibliographic review of aspecific Wassermann reactions, discusses the peculiar observation of a four-plus Wassermann sero-diagnosis in a girl aged 11 with hepatic distomiasis, in whom there were no signs pointing to syphilis and in whom the reaction soon became negative when, following intensive treatment, the daily search for ova of *Distoma* proved negative.

Newham (1927) describes a case in which the serum of a patient suffering from liver abscess gave a positive Wassermann reaction on the day after the abscess was evacuated as well as a week and two weeks later, but which was

completely negative to tests carried out three and four weeks after the operation. Syphilis could be excluded in this case, and the author believes that the reaction was due to the tropical abscess. He mentions also a case in which a tube containing a serum which was used as a negative control was on one occasion very slow in clearing. On enquiry he found that the patient from whom the serum had been obtained had an hour previously received a dose of carbon tetrachloride for ankylostomiasis.

Verdozzi and Urbani (1916) give a tabular and detailed account of twenty-six patients with chronic hepatic infections unassociated with syphilis. A positive reaction was obtained in twenty out of the twenty-six patients. Nine of the twenty-six were suffering from primary or secondary new growths of the liver, and eight of these gave a positive reaction, in seven the reaction was strongly positive.

Shunobu Matsumura (1934) tested the Wassermann reaction in 397 cases of malignant tumour, 336 carcinomas, and 61 sarcomas of different parts of the body. The reaction was positive in about a seventh of the carcinomas and about a fifth of the sarcomas. No clinical evidence of syphilis could be found in about half the cases of both carcinoma and sarcoma, and in many of them even no evidence at necropsy. They conclude that a positive Wassermann reaction does not necessarily indicate syphilis either in sarcoma or carcinoma.

Harrison and Osmond (1943) mention a number of references in the literature regarding the occurrence of false positives in glandular fever and after recent vaccination. They also refer to cases in the literature of transient bronchopneumonia, with very little constitutional disturbance, which may cause a positive reaction persisting for two months or more.

Kaufman (1941) found a false positive Wassermann reaction in glandular fever which persisted for as long as two months.

Chargin and Rein (1941) recorded a list of 253 'problem' cases. In some of these cases, in which the blood had sometimes been positive and sometimes negative no one had been able to say whether the person concerned had ever had syphilis. Cumming and others (1935) give the percentage of false positive reactions obtained by thirteen pathologists each employing his own method. These



varied from 42 per cent to 72 per cent in leprosy, 0 per cent to 77 per cent in tuberculosis, 0 per cent to 97 per cent in malignant disease, 0 per cent to 89 per cent in fever other than malaria, natural or induced, 8.6 per cent to 20.6 per cent in malaria, 0 per cent to 3.9 per cent in jaundice, 0 per cent to 3.8 per cent in pregnancy

Boas and Neergaard (1934) state that with the technique employed at the State Serum Institute (Copenhagen) a false positive Wassermann reaction in febrile pulmonary disorders seems to be rare (less than 0.33 per cent.), yet in view of the results of other investigations they advise a certain degree of caution in judging the serological test in the presence of an acute highly febrile lung disorder

Storp (1924) reports a positive Wassermann reaction during the course of a staphylococcal septicæmia in a child aged three years whose parents were free from syphilis. At the end of fifteen days the temperature fell to normal and the Wassermann became negative. In view of this case the author set himself to investigate whether an analogous phenomenon might not be observed in other septicæmias. He studied generalized streptococcal and pneumococcal infections, but found the Wassermann reaction to remain negative

### Other Factors Giving Rise to False Positive Results

Other factors which may cause pseudo-positive reactions are vaccination against smallpox, administration of animal sera, diphtheria antitoxin, etc., general anaesthesia, pregnancy, administration of certain drugs, high protein diet, serum of persons "in articulo mortis," and corpses, transient false positives in apparently normal persons with recent illness

*Diphtheria* —Frei (1929) confirmed the statement of Hentschell and Szegő that the sera of non-syphilitic patients can give rise to false positive syphilitic reactions after injections of diphtheria antitoxin

Boas and Tölböll (1932) tested by the Wassermann and Kahn methods the sera of a hundred patients before and after injections of anti-diphtheria antitoxin. All were negative before, and ninety-nine were negative after the injection of anti-diphtheria serum. In the case that was positive the patient received 80,000 units intra-

venously and 140,000 intramuscularly. The tests were carried out by separate assistants and became positive six days later. Eight days later the serum became completely negative

Stern (1932) states that there have been several reports of positive Wassermann reactions after injection of diphtheria serum. The accuracy of the observations cannot be doubted, but the author advises caution in their interpretation. He observed cases in which the diagnosis was diphtheria but in which the bacteriological examinations did not confirm the clinical impression. No antitoxin was administered in these cases, but in some of them a transient positive reaction of the serum for syphilis was obtained. Positive reactions for syphilis were also observed after Vincent's angina and infections with spirochaetes of balanitis. In other words, positive serological reactions for syphilis may occur after infections of the throat without the administration of diphtheria serum, but these usually disappear spontaneously. However, they may persist for longer periods if the infectious foci persist

*Anæsthetics* —In a few cases the sera of patients under general anaesthesia have been stated to show a positive reaction. Green (1923) investigated the effect of chloroform and ether upon the Wassermann reaction and the syphilis reaction of Dreyer and Ward. The anaesthetics had no effect upon either reaction. It is generally believed that anaesthesia increases the anti-complementary properties of the blood, special care being required in the performance of the Wassermann test to avoid false positive reports. The Kahn test, not being influenced by anti-complementary properties of serum, is still less affected by anaesthesia. There is no conclusive experimental evidence for the assumption that either test gives false positive reactions during anaesthesia. Nevertheless, as a factor of safety, no serological reaction obtained during anaesthesia should be depended on, particularly if not supported by clinical observations. At least forty-eight hours should elapse between a general anaesthetic and the drawing of blood for a serological test

*Lead Poisoning* —Dreyer (1911) obtained positive Wassermann reactions in certain cases of lead poisoning. In thirty-five cases examined, four showed a positive reaction although the men had never been syphilitic. Schnitter (1911) investigated sixteen workmen presenting symptoms of lead poisoning. Four showed a positive reaction, one of these men had suffered from syphilis three years before, although no symptoms of the disease existed at the time of examination. The men giving a positive reaction had been engaged in the lead work for periods varying from eighteen to forty weeks, and the others for periods of from two days to seven weeks, it is, therefore, probable that

the positive reaction in lead poisoning depends on the degree and the duration of the poisoning.

*Intravenous Injections of Colloidal Silver*—Since the Wassermann reaction is essentially a colloidal phenomenon, Picado (1917) felt it might be interesting to ascertain the effect of the intravenous injections of colloidal substances upon the reaction. It was found that colloidal silver influences the Wassermann reaction either by reactivation or by inhibition. It may even bring about a positive reaction in normal individuals. These facts must be taken into account in making examinations of persons recently treated with colloidal substances.

*Digitalis*—In order to verify Bauer's statement that administration of digitalis may produce non-specific positive reactions, Nicoletti (1929) carried out Wassermann tests in persons treated with digitalis preparations. He administered digitalis to forty-five Wassermann negative persons, in none of whom was a positive Wassermann produced.

*Quinine*—It has been stated that the administration of quinine may produce a transient positive Wassermann reaction, but this has not been confirmed.

*Iodoform Solution*—Gjorgjevitch and Pievatchevitch (1927) injected twenty rabbits intravenously with an iodoform solution. After ten or twelve injections the Wassermann reaction became positive in the blood of the animals and remained so for a few days. Subcutaneous injections had no effect. Eleven patients with a negative Wassermann reaction were injected intravenously with increasing doses (from 0.05 mg. to 0.25 mg.) of iodoform in 3 or 4 c cm. of water. The Wassermann reaction became positive after ten or twelve injections totalling 1.5 g of iodoform. A positive Wassermann reaction may, therefore, occur in patients with soft chancres treated for long periods by iodoform.

Green (1923) investigated the effect of various drugs—for example morphine, caffeine, amyl nitrate, epinephrine, pituitary extract—and of fat digestion and fever upon the Wassermann reaction and the reaction of Dreyer and Ward. They had no effect upon either reaction. He states that the presence of considerable fat in the blood causes the serum to become anti-complementary, a property it loses upon the mechanical removal of the fat.

*Corpses*—Bertolozzi (1934) carried out serological syphilis tests on fifty corpses. A positive reaction was occasionally observed in the serum of persons in *articulo mortis* and in that of a large percentage of corpses.

*Protein Diet*—Barnes and others (1943) record a case of strongly positive Kahn and Kolmer Wassermann reactions in a young student who denied venereal exposure. This student in the

course of work in a meat market had developed a habit of eating small pieces of raw meat picked up from the chopping block. On the possibility of a high protein diet being the cause of a false positive he was told to stop the practice. In a few weeks his serum became negative. These authors adopted the practice of putting persons whose sera gave contradictory results on a milk-free meat-free diet for three days, and they give examples of reversals of serum reactions after the institution of this regime, on the other hand they never succeeded in making the serum again positive by restoring the high protein diet.

*Sulphur dioxide*—Marsh (1945) recorded an instance of a "control" negative serum becoming positive after keeping a fortnight in a refrigerator. After a lengthy investigation he found that further specimens of sera originally negative gave positive Wassermann reactions when kept for a week or longer in a certain refrigerator. The refrigerator in question had been in constant use for over four years. No mechanical defect nor leakage of gas could be detected by the refrigerating engineers. The refrigerant was sulphur dioxide, and he suggests as a cause a leakage of gas too slight to be detected by ordinary engineering methods.

### Concluding Remarks

It may be asked whether there are any statistics in this country regarding the incidence of non-specific reactions with the Harrison-Wyler technique. I personally know of none, and should like to hear, during the discussion to follow, if there is any information on the subject.

In America, Stokes and others (1946), sponsored by the Committee on Medical Research and the Venereal Diseases Subcommittee of the National Research Council, give statistics over a nine-months' period regarding the occurrence of non-specific positive (so called "biological false positive") reactions for syphilis among Red Cross blood donors. In all 210,261 blood specimens were tested. Out of this number 489 (0.23 per cent.) gave positive results. Of 79 unselected donors with positive serological tests submitted to further extended clinical and special serological studies, only 40.5 per cent were finally adjudged by a reviewing board to have syphilis. The remainder, 59.5 per cent., were adjudged to have actual or probable false or non-specific reactions. In the process of evaluation a diagnosis of syphilis was reached in three months in 69.2 per cent, in non-specific positive cases 78 per

cent required more than three months for a decision

We now come to the question how best to guard against a false diagnosis of syphilis when an unexpected positive result is reported and where there are no clinical signs or history of syphilis. First, any technical laboratory error must be excluded by repeating the Wassermann tests in conjunction with a Kahn test, and submitting a specimen to a central laboratory or other reliable laboratory as a check

Harrison and Osmond (1943) recommend that any doubtful reaction obtained by the Harrison-Wyler modification should be subjected to the Richardson modification, which is said to weaken non-specific reactions and strengthen specific ones. Further, such sera should also be subjected to the Kahn Verification test with a view to determining whether the reaction indicates a specific or a non-specific type of reaction

While these tests may help, it must be recognized that we have no certain serological verification test at present. Let us hope that in the near future some specific physico-chemical test for non-specificity will be devised

### Summary

The serological warnings of non-specificity may be summed up as follows

1 Any consistent weak positive or doubtful but fluctuating reaction, sometimes seen with strong positives

2 Any serological variations and disagreement of results, when the tests are carried out by other laboratories

3 Negative Wassermann and positive flocculation reactions

4 Positive tests tending to become negative within a three-months' period on weekly repetition

The following safeguards are suggested

1 A very careful enquiry should be made respecting any recent illness or any other condition mentioned liable to cause false positive reactions

2 A positive result should not be regarded as an emergency before any diagnosis is made, except possibly in pregnancy, there should be a probationary period for at least three months before commencing treatment

3 A careful clinical examination, including radiography of the cardiovascular system, and cerebrospinal fluid tests, should be made

4 There should be careful investigation to exclude the possibility of congenital syphilis, including the examination of infants

5 There should be consultation with other venereal disease specialists, including the pathologist, before making a final decision

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## DISCUSSION ON THE PRECEDING PAPER

DR. G L M McELLIGOTT (the President) said he was interested to hear that the false positive Kahn reactions might possibly be caused by temperature, because this might explain certain discrepancies noticed between Kahn and Wassermann reactions during the recent cold spell. He was interested in what had been said about atypical pneumonia and had himself observed a case in which an x-ray opacity in the lung gradually vanished with the decline to negative of the false positive Wassermann.

Much had been said about false positives. He would also like to hear the speaker's views on false negatives. In many cases presented for an opinion the Wassermann was repeatedly negative, contrary to clinical findings.

DR. I N ORPWOOD PRICE said that when he thought of all the diseases which were said to be the cause of false positive Wassermann reactions he wondered why they bothered to do such a test. Most of this evidence came from abroad. Not very much had been produced in this country to show that false positive reactions were obtained from the diseases enumerated, and he felt that the many false positives reported must be due to faults in technique, not only in the Wassermann but also in the Kahn test. There was, moreover, little doubt that the Kahn antigen produced in America fifteen years ago was a better product than that produced now. He wondered whether commercial firms manufactured their Kahn antigen by mass production methods which yielded an antigen more liable to give false positive reactions. In his own experience a true biological false positive was uncommon. He wondered what all this evidence really meant. He worked with clinicians who were keen and who told him promptly if a mistake had been made. He was grateful for this co-operation, but if these false positives were so common he would have been told about them and would have had to do something. He had not studied a series of particular diseases, in fact he could think of only three types of cases which might have any bearing on the matter. First, mononucleosis and in this disease he knew of only one patient who gave a false positive reaction. This remained positive for about a fortnight, during which five different specimens of blood were taken, each test gave a very weak positive result except the last, which was negative. Secondly, he estimated that he had examined 10,000 routine specimens from pregnant patients. He had expected 3 per cent. to be

positive. In fact, up to the present, the rate had been about 0.05 per cent. Thirdly, he had thought that high fever might give a false positive reaction and when Mr King was at Westbury he supplied Dr Price with specimens of blood from patients who were undergoing high fever treatment. The specimens were taken at the height of the fever and of 80 tests all were negative except one. An American negro suffering from syphilis. He could not help thinking that a lot of nonsense was talked about biological false positives. He would not say they did not occur but that if they did the numbers would appear to be very small.

COL. L W HARRISON wished to endorse what Dr Price had said about the importance of technique. He believed that many false positives were the result of bad technique. A number of tests called Harrison-Wyler, carried out in this country had given very different results with the same sera from those obtained in the Venereal Diseases Reference Laboratory, where the H-W method was the standard. Some people who said they practised that method (and he was sure this applied to the Kahn and other well-known methods) did not practise it in all its details. He would like to have sent many of the serologists whose test methods had been compared with the standard used in the Reference Laboratory to school with Dr Wyler, who could distinguish and divide a hair twixt north and south west side. Dr Wyler was unhappy if anyone walked into his laboratory smoking a cigarette because he feared the anti-complementary effect of a flake of tobacco ash falling into one of his tubes. Many serologists might copy with profit his care of glassware and of his complement sera between titration and use in the test proper.

He thought that statements made by many authorities that pregnancy did not tend to cause false positives was based on slender evidence. Good evidence that it did so could be found in the Report of the first Serum Conference at Copenhagen, in which there are reports of tests carried out in separate laboratories between the date of the Paris Conference and that held in Copenhagen. Reports of the State Serum Institute and of the Warsaw Institute recorded many positives in pregnancy under the heading of patients without clinical evidence or history of syphilis. His own experience in the many comparisons of serum test methods carried out by the Ministry of Health's Venereal Disease Reference Laboratory between the two wars was that a shaky

test would be shown up by pregnancy sera more readily than by the normal sera commonly used for controls

If two or more tests were used, one should be a complement fixation test. At the Serum Conference in Copenhagen in 1928 he had argued this point with Dr Kahn, who had contended that one of the tests need not be a complement fixation. The opinion of the delegates was taken and representatives of seventeen of the twenty-one laboratories taking part in the Conference stated their preference for inclusion of a complement fixation test, he believed this view was held more generally today than it was in the early days of the more successful flocculation tests

There was value in doing the test quantitatively in cases under treatment and when there was any suspicion that the result was false. He would agree also that in any case of doubt a serum should be submitted to one or more other laboratories

DR T E OSMOND agreed with Dr Orpwood Price and Colonel Harrison on the question of technique. He thought that the Wassermann was the most abused test in pathology, and in this country it was performed incorrectly more often than any other test. Dr Thomson had referred to the fact that a positive Wassermann did not necessarily mean syphilis, yet hundreds of doctors wrongly thought otherwise.

He was interested in what Dr Thomson had said about the effect of protein. If a high protein intake was likely to produce a false positive, this should become less and less frequent in present circumstances. With regard to the number of false positives, he thought that possibly Dr Price had misunderstood what Dr Thomson had said. The fact that there were scores of diseases that might give, or were said to give, false positives did not mean that false positives were very common. Many of these diseases were tropical and did not occur in this country, and many were uncommon, any clinician should hesitate to accept a positive reaction in the presence of a disease other than syphilis. What was happening was that many pathologists had found a positive reaction in such and such a disease and reported it in the literature, implying that such and such a disease gave a false positive Wassermann reaction. The next writer quoted him as saying *X* disease produced a false Wassermann reaction and that was how the reputation had grown. A few years ago he had investigated carefully a considerable number of specimens from cases of scarlet fever without getting even one positive Wassermann reaction among them. One must distinguish between the false positive due to some definite disease other than syphilis, and the false positive which occurred in an apparently healthy person, the two things were quite different. If the patient was suffering from a particular disease one could wait until he had recovered and keep on testing his blood. One would expect to find some differences in a patient who had normal health, in syphilis the Wassermann might be double plus almost indefinitely, and that was where the quantitative test was valuable. False reactions did not usually give a

very high titre, and on repetition there might be a change up or down. If it was up it was important, but if it was down the verdict was against syphilis.

He had recently written a critical review of the literature on this subject, he would not repeat all he had said, but there were one or two points worth mentioning now. One was that there was an antigen known as "cardiolipin" being developed in the United States at the present time, and its use might eliminate some of the false positive reactions. It was a good idea to do two tests, and do them on separate specimens of serum taken from the same blood. The blood came in a tube from the clinic to the laboratory, and he insisted on his technician putting up two samples of each specimen, one for the Kahn and one for the Wassermann, so that any question of a mixture of specimens in the laboratory would be discovered.

Until the Ministry of Health issued its own supply of rabbit serum, many pathologists were using horse serum amboceptor, they did not realize that this led to false positive reactions.

Many people now believed the Kahn verification test was useless. When he started doing the Kahn test in 1922 he obtained his Kahn antigen directly from Dr Kahn and it was very good. Subsequently he made his own antigen from dried heart powder, and that apparently worked quite well. During the war when he was responsible for a great many blood tests he was very uneasy about the Kahn antigen supplied to the Army, and was quite sure that some of it was of poor quality. Recently he had again obtained a considerable supply of Kahn's own antigen and had found it excellent. It was insensitive rather than oversensitive. He was not prepared to give an opinion on the antigen being marketed in this country nowadays. In ninety-nine cases out of a hundred a positive reaction without clinical signs was not an emergency, and a decision could wait for three or even six months. It was better to wait and do a series of tests rather than come to a wrong decision and start treating a non-syphilitic patient for syphilis. A positive reaction which did not agree with the facts should be viewed with suspicion.

COL FAWKNER-CORBETT was critical of the suitability of some pathological specimens and their submission. It would be a great advantage if all new house surgeons were taught the correct way to take specimens. The next point was to get the right name or identification number on the specimen.

He was in complete agreement with what had been said with regard to the Kahn antigen. He had had cases in which spirochaetes had been found, the Wassermann had been positive, and the Kahn had been completely negative, consequently the Kahn test with him had fallen into disrepute. He also agreed on the question of having a flocculation test controlled by a fixation test. A quantitative estimation was of value in the latter test. He had known patients giving a positive result in whom there were no clinical signs. In one he himself had corroborated a previous positive finding, in the other his own positive

result had been confirmed at another laboratory. There were no clinical signs in either patient, but in each there was a history of syphilis in a maternal grandmother. He suggested that the Biblical reference to the sins of the fathers being transmitted to the third and fourth generation be kept in mind. Were the positive results in these two cases really false? Might not something have been transmitted which could cause a positive Wassermann reaction although there was no clinical evidence?

Two other cases had come before him which, lest clinicians rely too much on their house surgeons, might be borne in mind. The Wassermann reaction had been found strongly positive in sera from two patients, but, according to the medical officers, in neither were there any clinical signs. The specimens were re-tested and the same results were obtained. He therefore went to see the patients himself and found Hutchinson's teeth and scars of old interstitial keratitis in both cases. A thorough clinical examination was essential in trying to make certain whether a positive Wassermann reaction was true or false.

DR H. M. HANSCHALL said that most of the reports of a positive Wassermann test in non-syphilitic cases had come from the tropics, and the reliability of many of these tests had been more or less rightly disputed. Yaws hardly needed mention—it was most probably syphilis. There was the important and common tropical disease, malaria, and this infection had already, in these post-war days, passed unrecognized as such in men and women returned from war service in the tropics. It was a fact that malaria very often gave a clear positive Wassermann during the fever and sometimes for five or six weeks after its cessation. In consequence, some of these cases had been suspected of syphilis when blood tests had been done in the non-febrile period at which time malaria parasites were absent from the peripheral blood.

DR NEVILLE MASCALL said he felt he had been fortunate in the pathologists with whom he had associated. He started off with Dr Osmond and passed on to Dr Orpwood Price, and now he was with Dr Thomson. He had come to realize the value of close contact with the pathologist. For a time he was in the position where he was absolutely unable to get into touch with his pathologist and had to take his reports by post. Most of them came back anticcomplimentary. It was claimed that this was due to the results of posting. There must be many people in this country who were working under the same difficulties. As a clinician he would say that he thought the time had come when there should be a standardization of the reports of tests. Each pathologist's report was more or less different although there was a standard available for reports, it was not used.

Recently he had seen two examples which he thought were false positive reactions. The patients had now been watched for a period of six months and had both become negative. One

was a man who had recently been vaccinated. His Wassermann was never stronger than 1 plus, his Kahn was positive. There were no clinical signs of syphilis. He was closely watched and the Wassermann came down slowly, and the Kahn was also now negative. The other was a patient with lymphatic leukaemia for whom a splenectomy had been done in the Army, and he gave a positive Wassermann and Kahn reaction. He showed no evidence of syphilis, and after about three months his Wassermann and Kahn became negative. These two cases could be classified as giving false positive results, because the Wassermann and Kahn test were repeated so often that an error in technique would have been discovered.

The serological reactions of pregnant women had been a source of worry to him and he was afraid he did not agree with Col Harrison. He thought, on the whole, that the serum of pregnant women tended towards negativity. He had seen quite a number of women with negative Wassermann reactions who were delivered of syphilitic children. Something must have suppressed the disease, otherwise they would have given a positive result. There were many patients who had had the minimum amount of treatment to make their blood test negative but probably not sufficient to keep it negative. If there were a tendency to positivity during pregnancy, one would expect this type of case to revert back to being positive, but he never saw this happening. If there was the least suspicion of doubt regarding pregnant women, it was safer to treat them. He was opposed to treatment without definite evidence but if the husband was a known syphilitic and his wife had negative serological tests then that wife should be treated during her carrying period. Full treatment was surely worth while if the birth of a congenital syphilitic child could be prevented. He strongly advocated the treatment of all known syphilitic mothers during each pregnancy, whether their blood was negative or positive.

DR R. R. WILLCOX said that, if yaws was, as some suggested, the same disease as syphilis, the so-called false positives from this disease were in fact true positives. Within recent weeks he had seen a number of West Africans and of the last fifteen no less than five had strongly positive Wassermann and Kahn reactions with no clinical or historical evidence of syphilis. Yaws being a disease of childhood, it was not always possible to get a history but one of these sero-positive patients gave a history of yaws at the age of five. Dr Thomson had quoted Butler on the subject of the relationship of yaws and syphilis but it should be remembered that this author had been to some trouble to prove that yaws and syphilis were the same disease. This was partly wishful thinking as if this could be so proved, then a case could be made to show that syphilis was not brought back from America by Columbus' crew but, on the contrary, had been imported into America by the slaves.

COL. L. W. HARRISON said that on the question of pregnancy he thought he could agree with Dr Mascall. He emphasized that a shaky technique

would bring out false positives in pregnancy. Pregnancy might tend to weaken the real syphilitic reaction, pregnancy might in itself be a mild treatment for syphilis.

SQUADRON-LEADER NOBBS said that he had recently seen two warrant officers in the Royal Air Force who had positive Wassermann reactions and a negative Kahn test. The pathologist had suggested that these results might be due to the blood cholesterol content. This was tested, and found to be high, and he wondered if there was anything in the suggestion.

DR R. B. TAMPI said that in India, where most of the diseases listed by Dr Thomson were endemic, the false positive Wassermann reaction was a problem, particularly in areas where there was a great incidence of malaria. It was difficult for him to say whether these positives were technically or biologically false positives, but it had been his experience that one did get frequent positive reports in malaria in the acute stages and for about four weeks following the attacks. Positive results in chronic malaria were also seen.

Of all the diseases which gave rise to false positive reactions in that part of the world, he would consider yaws most important. Next to yaws came leprosy, particularly in what was called the lepromatous type, it was not so common in the neural type. It was unfortunate, because in certain types of leprosy the skin lesions were difficult to differentiate from the skin lesions of syphilis. The third disease was lymphogranuloma inguinale. He had found ten persons with this condition who gave a false positive which after a time became negative. He had not had much experience in the other conditions mentioned.

DR THOMSON, in reply, said he was glad to have the opinion of pathologists on the frequency of false positive reactions, because he had felt rather doubtful in his own mind about their frequency and the high incidence reported in the U.S.A. literature. He was averaging about 4,000 Wassermann tests a year, and it was very seldom that he obtained a false positive reaction. Occasionally he obtained a doubtful ( $\pm$ ) reaction which he did not place in the category of a false

positive reaction because when the tests were repeated they became negative. He was relieved that his brother pathologists supported his opinion that false results were not so frequent as was stated in the literature. Nevertheless, he felt that the possibility of false biological positives must be recognized and the clinicians must be on the watch for them.

He agreed with Dr Orpwood Price that the powdered beef heart material as supplied commercially for the Kahn test was very unsatisfactory. He had tried making up batches himself and had found that only one out of three or four batches had been satisfactory, which was disappointing to the technicians preparing the Kahn antigen. For this reason he was glad that there was a central laboratory where one could get the standard reagents. He thought that in the days when pathologists made their own antigens they got more false positives than they did now when using specially prepared standard reagents. He would recommend laboratories as far as possible not to make their own, but to get it from a central laboratory.

It was very difficult to explain the occurrence of negative Wassermann in cases of syphilis, where syphilis was definitely diagnosed. Sachs, who was a master of the serology of the Wassermann test, said that, although flocculation tests were usually more sensitive than the Wassermann reaction, occasionally the opposite might obtain. He said that the complement fixation and flocculation tests results were the consequences of the same alteration of the globulins, which might be caused either indirectly or specifically, although flocculation tests were usually more sensitive. The complement fixation occurred best when the antigen-antibody complexes were in the state of development, and this depended to some extent on optimum proportions similar to those intended to produce a flocculation reaction. On the other hand, complement fixation might be inhibited by non-specificity of the components. Because of these peculiarities, both Wassermann and Kahn tests should be used in the diagnosis of syphilis.

He could not answer the question whether a high blood cholesterol might cause false positive reactions. It was an interesting point, and there was probably something in it, it should be further investigated and the results published.

# NOTES ON THE INCIDENCE OF VENEREAL DISEASE IN THE BAHAMAS

BY

W P U JACKSON

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The Bahamas group of islands lie in the Caribbean Sea off the coast of Florida and are inhabited by some 60,000 people of whom the great majority are negroes of West African stock. At least one half of the native population live in a small area in the capital city, Nassau, in conditions of depressing squalor, filth, overcrowding, poverty, and ignorance. Nassau contains the Bahamas General Hospital—the only place in the island group at which pathological diagnostic and treatment facilities are available for venereal diseases. Incidentally, it may be recalled that Columbus first landed at San Salvador, an island of the Bahamas group, and there his crew may have acquired syphilis and later carried the disease back to the old world. The inhabitants in those days were Lucayan Indians.

The Bahamas are a lucky group of islands, for although they lie only just north of the Tropic of Cancer, they are spared most tropical diseases. Yaws does not appear, nor schistosomiasis, nor Leishmaniasis, nor trypanosomiasis. There is no malaria, despite the presence of Anopheline mosquitoes, no sandfly fever, despite myriads of sandflies, no yellow fever, although the Aedes, I understand, inhabits the island. Even ankylostomiasis does not exist because the soil is too porous to sustain the parasitic nematode (Beveridge, 1927). Leprosy is uncommon. The more temperate diseases, diphtheria and rheumatic fever, are not known. To make up for this, phthisis is a great scourge and tends to be exudative and rapidly progressive. Venereal diseases are almost the rule rather than the exception: syphilis, gonorrhoea, lymphogranuloma inguinale, and chancroid are all very common. Late syphilitic involvement of the central nervous system is very rare but that of the vascular system is common and

the local hospital even describes one or two cases per year of dissecting aneurism of the aorta due to syphilis.

## Civilian Native Population (Chronic Syphilis)

The performance of Kahn tests occupies a great deal of the working time of the pathological department at the Bahamas General Hospital. These examinations are made as a routine on all in-patients, on pregnant women who can be persuaded to attend hospital, on infants born in the maternity department, on volunteers for the police and serving forces on food-handlers, and on various other groups of people. The results of Kahn tests (Table I) include these routine examinations on persons in whom there was no reason to suspect the presence of venereal disease, and may therefore be considered as fair samples of the native community as a whole. Doubtful results are not included as positive unless definitely so on repetition. If doubtful reactions ( $\pm$ ) were also included (a procedure claimed to be legitimate by Parran and others, 1941) the figures for positive tests would be about 20 per cent. higher.

TABLE I  
INCIDENCE OF POSITIVE KAHN REACTIONS AMONG  
THE NATIVE COMMUNITY

Year	Total tested	Positive	
		Total	Per cent.
1939	5 489	1 453	26.4
1940	5 037	1 360	27.0
1941	5 163	1 075	20.8
1942	5,342	1 035	19.4
1943	4 760	826	17.4
1944	4,881	928	19.0

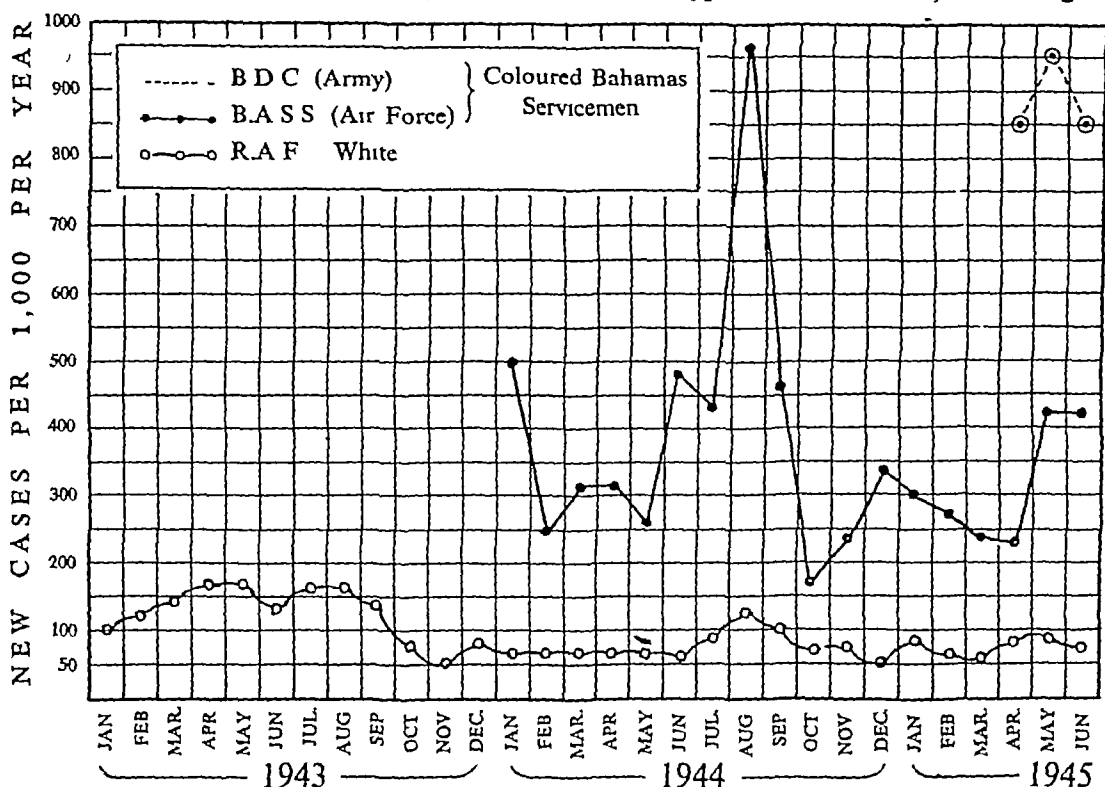


High though these figures are, the percentages of positive Wassermann reactions found among coloured draftees into the United States Army in the recent war were even greater in several states, e.g. 40.6 per cent in Florida, with an average of 27.2 per cent for all states (including doubtful reactions), (Vonderlehr and Usilton, 1942), while Keidel and Moore (1923) found an incidence of 22.9 per cent of positive Wassermann reactors among negroes in 5,000 in-patients at Johns Hopkins Hospital. Incidentally these figures for positive syphilitic tests may be compared with those concerning the Frei test for lymphogranuloma inguinale in the United States. In two series, among United States negroes, positive results to the latter test were found in about 40 per cent of cases (Gelperin, 1943, Beeson and Miller, 1944). It must, however, be remembered that the Frei test, once positive, remains so after the infection has cleared (Grace and Rake, 1943).

Some further details are available of the Kahn test results for the year 1943 in which, out of tests done on 414 pregnant women, 61 (14.7 per cent.) were positive. With regard to age, out of 200 consecutive people of both

sexes between the ages of 18 and 22, 46 (23 per cent) gave a positive result, and in the age group 30 to 40 positive results were found in 60 (30 per cent). In this year the male female ratio of positive reactors was very nearly 1:1. A point of interest here is the high rate of infection at the low age of 18 to 22, and only a small increase in the infection rate among the 30 to 40 age group, the figures in both cases referring to the unselected general population. This contrasts with the negro rates in the United States, where 19.1 per cent. of Army draftees aged 21 to 25 drawn from all states had positive Wassermann reactions, while for the age group 31 to 35 the incidence had risen to 35.7 per cent (Vonderlehr and Usilton, 1942). Incidentally the corresponding white rates were 1.0 per cent. and 3.7 per cent—an even greater proportional difference.

Great difficulty was experienced in completing the treatment of syphilis in these coloured patients on account of their defaulting. Thus, at the Bahamas General Hospital, the average number of injections of an organic arsenical per patient was 6.3 and of bismuth 9.5. Smilie (1943) remarks that "among the whites syphilis has become, in the great



majority of cases, a disease of the ignorant, the careless, the criminal, and the social outcast," but it is evident, as Fullilove (1943) pointed out, that this applies to syphilis in any group of people, and to negroes as a whole, who are discriminated against economically and educationally. Following the advent of penicillin, which has shortened the course of treatment, a great reduction in the incidence of syphilis in the comparatively closed Bahamian community should result, but its eradication will have to await a very great raising of the living and educational standard of the coloured population.

### Royal Air Force

In 1942 a large Royal Air Force unit was formed in the Bahamas and based on Nassau. It consisted of some 3,000 white troops and, from January, 1944, of a contingent of coloured men attached thereto, some 270 strong (Bahamas Air Service Squadron "B.A.S.S.") In April, 1945, the R.A.F. Medical Service also started to look after the local coloured Army contingent of 360 men (the Bahamas Defence Corps "B.D.C.") The prevalent venereal diseases were syphilis, gonorrhœa, lymphogranuloma inguinale, non-gonococcal (or unproven) urethritis, balanitis, and soft sores. Many of the latter were examples of the chancroid caused by *Ducrey's bacillus*, which, until discovered in 1945 in the pathological department of the R.A.F. Hospital at Nassau, was not known to exist in the Bahamas. Because of this late discovery the exact number of true soft chancres in this series is not known.

The graph shows the monthly incidence of new cases of all types of venereal disease diagnosed in the white and the coloured contingents separately, the figures being reduced to show cases per 1,000 per annum. The high rate in August is interesting—it occurs in both white and coloured groups and shows an incidence in the coloured group (B.A.S.S.) of almost 1,000 per 1,000 per annum. August is the hottest and most humid month in the year in the Bahamas but contains no particular local festivities or orgies which might account for increased promiscuity. Gonorrhœa seemed to be the disease particularly affected in the peak but monthly figures for individual venereal diseases were too low to admit of any certain conclusions. Table II shows the relative frequency of the different venereal diseases, with a high proportion of syphilis among the white troops.

These rates compare unfavourably with those of the Allied troops in the Middle East, whose overall incidence of venereal disease in early 1943 was 30 per 1,000 per annum, or 18 per 1,000 considering British and Dominion troops only (Lees, 1946). The overall United States Army venereal disease rate in 1943 was 25.0 per 1,000 having been 42.5 in 1940 (Turner, 1943), and that of the British Army 11 per 1,000 per annum between 1940 and 1943 (Grigg, 1943).

### Control and Treatment

Attempts to reduce the incidence of venereal disease among white troops were made by lectures to the newly arrived men, by strict enforcement of the "out-of-bounds" limits which included the native quarter of the city,

TABLE II

RELATIVE FREQUENCY OF DIFFERENT VENEREAL DISEASES IN WHITE AND COLOURED TROOPS

	Total Cases			Ratio		
	Gonorrhœa	Syphilis	Lympho-granuloma inguinale	Gonorrhœa	Syphilis	Lympho-granuloma inguinale
White (3,000 men) (Feb 1943 to Jan 1945 incl.)	197	91	53	2.2	1	0.6
Coloured (270 men) (Feb 1944 to Jan 1945 incl.)	53	10	16	5.3	1	1.6

and by the provision of "early treatment" rooms with the usual facilities supplied in the Services. Attempts were made to persuade the local authorities to enforce the law which penalized infected women who had further intercourse, and also to persuade such women to submit to treatment, but without much success. These women were very difficult to trace because they could, and did, move their wooden homes on wheels overnight from one end of the native quarter to the other. Co-operation between the medical and the Provost Marshal's departments was considered very important, and there is no doubt that the excellent work of the latter department prevented much venereal infection.

The treatment of lymphogranuloma inguinale in men in the Royal Air Force in the Bahamas, especially from its surgical aspects, has been discussed by MacLaughlin (1945). The response to sulphadiazine (25 to 30 g in five days) was found to be good. Only 13 cases out of 68 required two or more courses, 8 relapsed within six months, 4 required aspiration or more drastic surgical procedures, and 4 were moved from the Bahamas during the observation period.

Chancroid was found to respond even better to sulphadiazine in similar dosage, there being no chronic sequelæ or relapses. Satulsky (1945), and Combes and others (1943), with much larger numbers of patients, obtained similar good results using sulphathiazole.

Acute gonorrhœa on the whole responded well to sulphathiazole or sulphadiazine, (Table III). Dosage was g 8 - 6 - 6 - 6 on

successive days, and the patients were followed up for six months, except when they had left the Bahamas before this period ended. Thus, until mid 1945, when penicillin therapy was instituted initially as a routine, there had been no evidence of sulphonamide resistance in any gross degree. McElligott (1945) remarks that negroes with gonorrhœa respond more favourably to all forms of treatment than do white men, and certainly even here the percentage of resistant infections in white patients was almost double that in the coloured men, but the figures are too small to be significant.

### Conclusion

These brief notes, with rather small figures, are intended partly as a record and partly to show that there is very considerable room for improvement in the venereal disease position in one of our colonies, which is incidentally a favourite winter resort.

I should like to thank Squadron-Leader B. Goodrich, who was in charge of the Venereal Disease department of the R.A.F. Hospital for part of the period referred to, and also the Chief Medical Officer of the Bahamas for permission to use the data obtained from the Bahamas General Hospital.

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TABLE III  
RESULTS OF TREATMENT OF GONORRHOEA WITH  
SULPHATHIAZOLE OR SULPHADIAZINE

	White		Coloured	
	Total	Per cent	Total	Per cent
Total men	198	—	65	—
Cured by single course	156	78	48	72.5
Cured after two courses	175	88	61	94
Single relapses	6	3	1	1.5
Sulphonamide-resistant	17	8.7	3	4.6
Left the Bahamas during observation period	21	—	0	—

# THE USE OF RICHARDSON'S MODIFICATION OF THE MINISTRY OF HEALTH'S STANDARD WASSERMANN REACTION (HARRISON-WYLER) AS A VERIFICATION TEST

BY

A C T VAUGHAN

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The 'ideal' serological test for syphilis, giving maximal sensitivity with absolute specificity, has still to be evolved, indeed, owing to the widespread distribution of 'Wassermann type substance' (Weil, 1941) it is doubtful whether the second requirement can ever be attained, the malarial patient, for instance, is long likely to give at least a short-lived reaction with the various serological tests for syphilis (Burney and others, 1942)

Normally there is an inverse relation between sensitivity and specificity, and in order to preserve the latter at a workable level sensitivity has been deliberately curtailed. The Ministry of Health's standard Wassermann Reaction (Wyler, 1929), which gave good results in the International Conferences held at Copenhagen in 1923 and 1928, is according to present day standards, relatively insensitive, but its chief fault lies in the rather large number of doubtful reactions which are given with both syphilitic and non-syphilitic sera. Subsequently it was shown that by the use of larger amounts of patient's serum the sensitivity of the test could be increased some 20 per cent without any reduction in specificity (Wyler 1932, confirmed by Fairbrother, 1933). Recently Richardson (1940) introduced a further modification of the standard technique which he claimed not only enhanced specific reactions but at the same time weakened the non specific thereby increasing both the sensitivity and specificity of the test.

For every serological system there is a definite ratio, the optimal ratio, of antigen-antibody concentration at which aggregation occurs most rapidly (Marrack, 1938). Marked departure of either reactant from this ratio may lead to inhibition of the reaction, the so called zone phenomenon. This is well shown in the precipitin reaction in which visible particulation is suppressed by large excess of antigen.

The optimal ratio for precipitation does not coincide with that for maximal complement fixation. The former occurs in the zone of slight antigen excess, whereas the latter is favoured by the presence of slight antibody excess (Dean, 1912). Complement is fixed during the early stages of particulation, therefore fixation is most rapid at the optimal ratio for the system, and becomes slower the greater the distance from this point in either direction (Goldsworthy, 1928).

In the standard Wassermann, using alcoholic tissue extract diluted 1/15 for antigen, with syphilitic sera of minimal reactivity the reaction takes place deep in the 'post zone' of antigen excess, where particulation is slowed if not suppressed and hence the fixation of complement is delayed or may not take place in detectable amounts during the period allowed for fixation to occur. This state of affairs leads to weak or false negative results being registered with such sera. On the other hand the comparable 'pro-zone' due to antibody

excess is not appreciable even with highly reactive sera (Wadsworth and others, 1938)

For this reason many workers (Eagle, 1936, Boerner and Lukens, 1937, Kolmer, 1937) have recommended that the optimum dilution, that is, that which detects the smallest amount of "antibody," should be found by experiment for each batch of antigen as prepared. Richardson (1940) explored "the possibilities of using stepped combining proportions of serum and antigen with constant complement." He advocates what amounts to the setting up of an additional tube in the Ministry of Health's test, in which the conditions of the reaction are so adjusted, by doubling the volume of patient's serum (thus following Wyler's suggestions (Wyler, 1932) for increasing sensitivity) and by the use of a greater dilution of antigen, that something approaching maximal fixation of complement by sera of low reactivity takes place in or near the zone of equivalence, at the same time non-specific fixations due to "impurities" in the antigen are diluted out.

In this paper an account is given of the results obtained by the use of Richardson's modification in the examination of those sera which gave weak or doubtful reactions with the standard technique, out of 3,826 unselected (but not consecutive owing to gaps caused by leave etc.) sera sent for examination to this Institute during five months in the first half of 1944. For the majority of sera the result of the standard Kahn Test (Kahn, 1928) was also available for comparison. Richardson's claim that by his modification the Bordet-Wassermann, as presented by Harrison and Wyler (Wyler, 1929) has been rendered considerably more sensitive without significant loss in specificity, appears to be fully substantiated.

The modified test deserves widespread adoption in this country wherever the Harrison-Wyler technique is in use, for great advantage can be obtained at little extra cost or trouble. The results also furnish additional circumstantial evidence (if this be still needed) of the essentially antigen-antibody-like reaction which takes place between lipid tissue extract and the reacting substances in syphilitic sera (Eagle, 1937).

#### Procedures

The Harrison-Wyler is the standard Wassermann technique in use at the R A F Institute of Path-

ology and Tropical Medicine. The tests were carried out on two mornings a week. All sera which gave weak or otherwise doubtful reactions were retested in the afternoon by the modified technique. For the standard test the directions contained in the Medical Research Council's Special Report No. 129 were closely followed. Such minor differences as existed will be noted. Donald's nozzles for dropping were used for adding the reagents, and were found to be both speedy and accurate; graduated pipettes were, however, preferred for the complement titration.

**Patient's serum**—The sera received for examination came from various R A F Hospitals and sick quarters. Strongly lysed or heavily infected sera were discarded. Sera waiting to be tested or retested were kept at 4° C. Inactivation at 55° C. for half an hour was carried out the day before the test. The Kahn test, when performed, was done on the afternoon before the Wassermann test.

**Complement**—Pooled lyophilized complement (from a commercial source) was used. A small quantity of salted complement (Richardson, 1941) was also tried. Both were found to be very satisfactory and kept well in sealed tubes in the cold. Haemolytic activity was always titrated on each morning of the test. While in use it was kept on the bench in a stoppered tube immersed in iced water.

**Antigen**—The alcoholic extract of beef heart was obtained from the Ministry of Health Laboratory. The diluted antigen for the standard test was prepared by adding quickly 14 volumes of saline to 1 volume of the cholesterolized (0.4 per cent) heart extract, after thorough mixing it was left to "ripen" for at least half an hour before use.

**Haemolytic system**—A fresh supply of sheep cells was obtained from a commercial source each week. After washing, a 3 per cent suspension by volume was sensitized with 6 M H D of anti-sheep rabbit haemolysin.

**Complement titration**—In order to obtain prompt lysis in the test proper, the minimal haemolytic dose was measured by observing the highest dilution of complement which showed complete haemolysis.

**Standard Wassermann (Wyler, 1929)**—Known positive and negative sera were included in each batch, as well as the usual reagent controls. The 2 M H D serum control was omitted, as it was found that by using it many sera were classified as anticomplementary which gave readable results with a 3 M H D serum control. A similar conclusion was reached by Webb (1936) when using the Kolmer 2-tube complement fixation test.

**Reading.**—As soon as the 3 M H D serum controls had lysed, usually after 7 to 10 minutes incubation in the 37° C. water bath the degree of lysis (or its complete inhibition) was noted in the test rows. As the average batch of sera under test was too large to allow of their all being read at this precise moment, the practice was adopted of leaving them in the water bath for half an hour, when a final reading was made after they had all been removed. There is some theoretical justification for allowing the complement to act on the sensitized cells for the same length of time as used in its titration (Eagle 1937).

Positive reactions after 10 and 30 minutes of incubation were graded as follows

*Strongly positive* (+ +) complete inhibition of lysis in both 3 and 5 M H D tubes

*Positive* some degree of lysis in the 5 M H D tube but complete inhibition in the 3 M H D tube.

*Weakly positive* complete lysis in the 5 M H D tube and some degree of lysis (up to approximately 50 per cent.) in the 3 M H D tube

In addition fleeting reactions ( $\pm$ ) at 10 minutes were noted

All sera which gave the following results in the standard test were re-examined the same afternoon by Richardson's modified test

- 1 After 30 minutes incubation weak reaction
- 2 After 10 minutes' incubation (a) positive (these usually became 'weak' or negative after 30 minutes), (b) weak reaction (usually negative at 30 minutes), (c) fleeting ( $\pm$ ) reaction
- 3 Any result which did not agree with the Kahn
- 4 Any result which seems to differ from that expected by the clinical history
- 5 Any serum which had given variable results in previous tests

### The Modified Test

The procedure of the modified test is summarized in Table I, for full details the original paper must be consulted (Richardson, 1940)

It will be seen that Row 1 constitutes the modified test. Row 2 is just the 3 M H D tube of the standard test over again and serves both as a reading comparator and as a check on any change that may have taken place in the reagents since their use in the morning. Row 3 is the serum control and therefore contains the increased volume of serum.

Complement containing 3 M H D was used throughout. After the addition of the sensitized cells a careful watch was kept on the behaviour of the sera under test. This was now possible because in the morning the standard test had eliminated all sera giving unequivocal results. It was rare that more than a dozen sera needed re-examination.

**Reading.**—If the fixation recorded in the standard test had been caused by "impurities" in the antigen, then the tube in the first row showed more rapid lysis than the middle tube and the result was read as negative.

In specific reactions the reverse sequence of events occurred, compared with the middle tube, lysis in the front tube (in Row 1) occurred more slowly, if at all. The classification of difficult sera with a low degree of reactivity was greatly facilitated by this direct comparison of the modified test

TABLE I  
THE MODIFIED TEST

Row	Serum	Saline	Complement containing 3 M H D per unit vol	Lipoid emulsion diluted		Sensitized RBCs
				1/15	1/120 <sup>1</sup>	
	vol.	vol.	vol.	vol.	vol.	vol.
3	2/5	1+3/5	1	—	—	1
2	1/5	1	1	1	—	1
1	2/5	3/5	1	—	1	1

1 vol = 0.11 ml = 2 drops from No 30 Starrett gauge dropper { saline complement sensitized cells 1/120 antigen emulsion

= 2 drops from No 18 Starrett gauge dropper { 1/15 antigen emulsion

1/5 vol = 0.022 ml = 1 drop from No 56 Starrett gauge dropper { Saline serum

<sup>1</sup> The Ministry of Health antigen at this dilution (1/120) gave "complete absence of lysis with strongly reacting syphilitic sera and something near the optimum fixation with weakly reacting syphilitic sera" and at the same time weakened non-specific fixation. Antigens with a constant (e.g. 0.4 per cent.) cholesterol content optimally sensitized with lipoid are of comparable "strength" (Kent, 1942). The 1/120 dilution was prepared by taking the 1/15 antigen used in the morning and further diluting it eight times with saline. According to Richardson (1940) "since the dilution is always carried out on a pre-formed lipoidal emulsion (itself constant) the exact change of hapten strength is reproducible from day to day."

<sup>2</sup> Magnesium ion was not added to the sensitized cells as it did not seem to have any appreciable effect on the rate of hemolysis.

with the standard (both tubes containing complement of identical hæmolytic activity and subject to the same conditions of incubation)

The results were recorded as positive (i.e. as "diagnostic" of syphilis) if at the end of half an hour of incubation the front tube showed complete inhibition (or only slight occurrence) of hæmolysis. The middle tube was usually more hæmolysed, sometimes completely so.

In a weak, but nevertheless significant reaction (see later), lysis in the front tube was partial or nearly complete at 30 minutes but always occurred much more slowly than in the middle tube.

**Results**—During 40 sessions 3,826 sera were examined, an average of 95.6 sera per session. This is rather more than the optimal number, but a very competent technician carried out the tests with assistance, and the only difficulty experienced was in reading the weaker reactions as their serum controls cleared. The standard test was always completed by midday. Ten sera were found to be anticomplementary and are excluded from further discussion.

The evaluation of serological tests based on a comparison of the results obtained by the examination of a series of unselected sera is rendered difficult by the absence of any practicable objective standards, save in the early primary stage, on which to base a diagnosis of syphilis (Wadsworth and Brown, 1936, Gilbert and Maltaner, 1945). An attempt, however, was made to classify on clinical grounds all the sera examined as either

syphilitic or non-syphilitic. The results, being thus based on data open to subjective error, have no absolute value and cannot legitimately (except as an indication of broad trends) be compared with those of other workers (see Table II).

The results obtained by the examination of these sera by the various ways described above are summarized in Table III.

It must be emphasized that neither sera which after 30 mins. secondary incubation in the standard technique were positive or strongly positive, nor those which lysed at the same rate as their serum controls (that is, clear-cut negatives) were retested by the modified method if the results were compatible with the clinical history. But it is not considered that even if the composite test had been carried out on all the sera, any marked change in the above figures would have resulted. The reason for not making the full comparison was to prevent overburdening an already hard-worked staff.

Table III shows (as far as the small numbers will allow) that the increased sensitivity of Richardson's modification test is not obtained at the price of specificity. In order to bring out this enhancement of sensitivity more sharply, the results with lowly reactive sera from known syphilitics are set out in Table IV. The majority of the patients had received varying amounts of treatment.

From these results (Tables III and IV) the following deductions may be made:

1 The modified test is much more sensitive than the standard test and with little loss of specificity. If the number of patients, rather than specimens of sera, giving false positive reactions be considered, the specificity of the Richardson modification is considerably improved: 0.09 per cent (3 patients) for positive results and 0.12 per cent (4 patients) if weakly positive results are included (see Table III).

2 Partial fixations in the modified test thus have a specificity denied to those obtained with the parent technique.

3 Results obtained are comparable with the standard Kahn test. The Kahn appears to be rather more sensitive in early untreated primary syphilis, but this is not an important advantage because the diagnosis may usually be more satisfactorily made in these cases by the demonstration of *Treponema pallidum* in the primary lesion. In older untreated

TABLE II  
CLINICAL CLASSIFICATION OF SERA

Number of sera giving positive (that is, "weakly positive" and stronger) reactions with either complement fixation or Kahn flocculation test	503
Number of sera giving negative reactions	3,313
Total	3,816
False positive sera (from history and clinical examination)	18
False negative sera ( <i>Treponema pallidum</i> seen in primary lesion)	8
Number of presumed syphilitic sera (503-18+8)	1,493
Number of presumed non-syphilitic sera (3,313+18-8)	3,323
Total	3,816

<sup>1</sup> 470 of these were also examined by the standard Kahn test in addition to the complement fixation reaction.

TABLE III

COMPARISON OF THE SENSITIVITY AND SPECIFICITY OBTAINED FOR THE WASSERMANN (STANDARD AND MODIFIED) AND THE STANDARD KAHN

Test	Standard Wassermann Reaction				Standard + modified Wassermann		Kahn
Duration of secondary incubation	30 mins		10 mins		see text		
Strength of reaction	++, +	++, +, ±	++, +	++, +, ±	+	+, ±	+++, ±
Sensitivity	55% (271)	58.4% (288)	62.7% (309)	73% (360)	83.6% (412)	91% (451)	93.4% (439)
Specificity	0.12% (4)	0.18% (6)	0.18% (6)	0.54% (18)	0.15% (5)	0.21% (7)	0.21% (7)

Figures in parenthesis = number of sera out of the total examined (493 for complement fixation and 470 for Kahn) giving the reactions indicated

Strength of reaction = as defined above p. 79

Sensitivity = percentage of the 493 syphilitic sera which gave positive reactions with the technique indicated (470 for the Kahn)

Specificity = percentage of the 3,323 non-syphilitic sera which gave (false) positive reactions with the technique indicated. Not all the 3,323 Wassermann negative sera were tested by the Kahn method so that the percentage for the specificity given for the Kahn is a minimum value

TABLE IV

SYPHILITIC SERA GIVING NEGATIVE OR WEAK REACTIONS IN THE STANDARD TEST BUT WEAKLY POSITIVE OR STRONGER WITH THE MODIFIED TEST

	HW 30	HW 10	HR	Kahn
A Congenital syphilis Young adults, treated	1/17 (5.9%)	9/17 (47%)	17/17 (100%)	13/16 (81%)
B Acquired syphilis				
(i) Untreated primary				
(a) <i>Treponema pallidum</i> seen	1/23 (4.3%)	5/23 (21.7%)	7/21 (33.3%)	12/23 (52.2%)
(b) Sero positive but <i>Treponema pallidum</i> not seen	2/12 (16.6%)	8/12 (66.6%)	11/12 (91.6%)	11/12 (91.6%)
Total untreated primary syphilis (a and b)	3/35 (8.6%)	13/35 (37%)	18/33 (54.5%)	23/35 (65.7%)
(ii) Treated primary and secondary syphilis	15/188 (8.0%)	153/187 (81.8%)	153/187 (81.8%)	139/166 (83.7%)

HW 30 = Harrison-Wyler (i.e. Ministry of Health's standard technique) read after 30 minutes' secondary incubation

HW 10 = Harrison Wyler read when 3 M.H.D. serum control had completely lysed (this was usually after about 10 minutes' secondary incubation)

H.R. = Richardson's modification of the Harrison-Wyler

Kahn = Results of Kahn test on (most of the) same sera for comparison.

The results are expressed as a fraction: the numerator represents the number of sera giving a serologically diagnostic result (weakly positive or stronger in a known syphilitic) and the denominator the total number of sera examined by the particular technique: the percentage positives are enclosed in brackets.



primary syphilis both tests are apparently of equal sensitivity, but the numbers concerned are too small for definite conclusions to be made

4 The standard test, if read after 30 minutes' secondary incubation, is only moderately sensitive but has a satisfactory degree of specificity

5 The standard test, read (as directed by Wyler, 1929) as soon as the serum controls clear, has a better sensitivity, but the percentage of false positives among the partial fixations is considerably increased so that only weak results in known syphilitics may be considered significant (see Table IV)

### Discussion

The modern tendency in routine work is to supplant the Wassermann reaction by a more easily performed flocculation test, and it is claimed that the advantages gained from doing two tests do not compensate for the extra work involved, particularly when some of the methods for performing the Wassermann in current use give inferior results (Kahn, 1940). This is probably true for small remote laboratories, but in large central reference laboratories it is desirable that results should be cross checked by the use of two tests. And if, as Weil (1941) points out, a complement fixation test be combined with a flocculation test, an increased number of positive results are obtained owing to the somewhat different ranges of sensitivity possessed by the two different types of reaction. Thus, of the syphilitic sera with low reactivity which are considered in Table IV, 12 per cent. were Richardson-positive but Kahn-negative, in 16 per cent the results were reversed (see Table V)

These divergent results are probably significant, since they were obtained in known cases of syphilis undergoing treatment. Webb (1936) came to the same conclusion. Berger and Sutherland (1944) obtained higher percentages for discordant results when testing a larger number of sera with the Standard Kahn and the Harrison-Wyler Wassermann method modified by the use of an optimum antigen dose. The relatively fewer discordant results in the present series may follow the use of pooled complement, thereby eliminating

day-by-day variation in the deviability of complement—an important cause of such discrepancies

The Wassermann reaction has the great advantage of an easily visible indicator system. The Kahn, probably the most reliable of the various flocculation techniques, suffers from the difficulty of reading the weaker reactions: there is an almost insensible gradation in particle size from the positive through the doubtful to the negative reaction, so that magnification except by low power (as Kahn himself insists) is of no help.

In order to obtain consistent results reading of the Kahn should always be done under standard conditions (such as the use of concealed artificial light against a dark background) which, having been adjusted to suit, should always be kept constant for any one observer. Even then, the Richardson test was found to be of more help in checking weak Kahn reactions than the reverse. The deliberate use by Richardson of the zone phenomenon to differentiate specific from non-specific reactions makes his modification a valuable "verification test," easy to read, and more readily carried out than Kahn's own verification test (Kahn, 1940).

TABLE V

COMPARISON OF PARALLEL WASSERMAN (RICHARDSON MODIFICATION) AND KAHN TESTS ON SYPHILITIC SERA

HR	Kahn	Sera of low reactivity (see Table IV)	Syphilitic sera subjected to both complement fixation and Kahn (see footnote in Table II)
		No	No
+, ±	++, +	132 (66.7%)	404 <sup>1</sup> (86%)
+, ±	—	25 (12.6%)	25 (5.3%)
—	++, +	33 (16.7%)	33 (7%)
—	—	8 <sup>2</sup> (4%)	8 <sup>2</sup> (1.7%)
Totals		198 (100%)	470 (100%)

HR +, Kahn ++ = positive reaction.

HR ±, Kahn + = weakly positive reaction.

<sup>1</sup> includes 272 Kahn positive sera which gave positive or strongly positive readings with the Standard Wassermann.

<sup>2</sup> These sera although negative to both techniques were obtained from patients in whose primary lesions *Treponema pallidum* was demonstrated.

It must not be forgotten that the antigen is the most important reagent in serological tests for syphilis, and any general improvement in specificity must now await its further fractionation. For instance cephalin which possesses strong anticomplementary qualities (Wadsworth and others, 1934), may be removed by ethereal extraction with apparent improvement. But the preliminary elimination of ether-soluble substances prior to the alcoholic extraction of normal bovine heart muscle is not carried out in the preparation of the McIntosh and Fildes' antigen used in the Standard Harrison-Wyler Wassermann technique. Richardson (1940) believes that 'impurities' play a part in producing a stabilized haptene emulsion, and relies on the effect of dilution to cause weakening or disappearance of any non-specific reactions caused by them. This seems to be justified, since it was found both in the present investigation and by Berger and Sutherland (1944) that the majority of partial fixations are specific when diluted antigens are used. It is interesting to note in this connexion that Hecht (1945) found that previous ethereal extraction of tissue produces an antigen of inferior value. The most effective fraction of dried beef heart appears to be one soluble in acetone and petrol ether. Moreover, he suggests (like Richardson) that use may be made of the "impurities," that is, the petrol ether and acetone insoluble fraction, in verifying non-specific "positives," since they give a stronger reaction with non-syphilitic sera (but weaker with syphilitic) than do the "specific" antigens. It is possible that cultures of non-pathogenic spirochaetes closely related to *Treponema pallidum* may be used to provide an antigen, but experiments in this direction have so far been only partially successful. Non-specific fixations are common, in experimental human *P. vivax* infection Eagle and others (1941) found that spirochætal antigen derived from the Reiter strain gave more biological (false positive) reactions than the use of lipid mammalian tissue extract in his own Wassermann and micro-flocculation techniques.

Of the factors tending to depress the greater inherent sensitivity of the complement fixation test, to which Berger and Sutherland refer in their paper (Berger and Sutherland, 1944), that due to variations in the deviability of the complement used (and which may, therefore,

affect whole batches of results) may be eliminated by the use of pooled complement from which unsatisfactory guinea-pig sera have been excluded. The large-scale issue of this pooled complement, either lyophilized or salted, would do much to make the performance of the Wassermann easier and more reliable. For factors present in certain individual sera which tend to lower the sensitivity of the Wassermann, central laboratories could try to eliminate the 'complementoid' effect (Ehrlich and Sachs, 1902) which sometimes 'antagonizes' the fixation of complement by weakly sensitized antigen that is, with a lowly reactive sera (Bordet, 1939), by precipitating it out in the carbon dioxide insoluble fraction of heat-inactivated serum (Berger and Sutherland, 1944). The occasional excess of natural antishæp hæmolysin may be removed by absorption with unsensitized sheep red cells, the use, however, of a well sensitized (6 M H D) hæmolytic system renders it less liable to be affected by the presence of natural hæmolysins in the patient's serum.

For the standardization of the cells it is more logical to use a method based on volumes, such as the measurement of a known volume following centrifugation of the thrice-washed cells to a constant volume, than to rely on the hæmoglobin estimation recommended in the Ministry of Health method (Wyler, 1929). Hæmolysin possibly acts on the monolayer lipoprotein membrane investing the red blood cell (Schulman and Rideal, 1937) and the liberation of hæmoglobin is a passive accompaniment of its destruction.

Finally a word may be said about the method of reporting results. Most of the so-called quantitative methods of performing the Wassermann test give only an approximate estimate of the 'antibody' titre, and the same applies, only to a higher degree, to flocculation tests: the amount of precipitate is not a true index of reactivity (Gilbert and Maltaner, 1945), so that, while the modern tendency to ignore roughly quantitative findings (expressed in the plusses beloved of old by serologists) and to report a result as simply 'positive' (i.e. diagnostic), 'doubtful' (significance depending on clinical assessment), and "negative" must in many ways be considered an improvement, inconsistencies still remain. The performance of a

strictly quantitative test, expressing the result as a figure directly related to the true "antibody" content would be even better. The serologist is concerned with the accurate measurement of antibody titres, (Maltaner, 1940) the clinician with its interpretation (Wadsworth and others, 1938). No positive serological result of the approximately quantitative type can be considered diagnostic on its own merits. Many causes of what are sometimes called "biological" positives are known. Malaria, leprosy, yaws, relapsing fever, vaccinia, infectious mononucleosis, and pregnancy may be cited. But Maltaner (1940, 1941), using a strictly quantitative complement fixation test, was able to establish a close serological relationship between syphilis and yaws, whereas with the same technique sera from lepers was readily distinguished from the sera of syphilitics by its uniformly low titre with a cholesterolized tissue extract as antigen.

### Summary

A brief account is given of the employment of Richardson's modification of the standard Harrison-Wyler Wassermann technique as a verification test for those sera which gave doubtful results with the standard test. By this means the sensitivity of the complement fixation reaction was considerably increased without any loss in specificity. This was particularly noticeable in sera from patients undergoing treatment, and is felt to be an important improvement (where serological tests are included among the various "tests of cure") in a disease such as syphilis, where it is doubtful whether clinical cure is ever accompanied by the complete eradication of spirochaetes from the body.

Compared with the standard Kahn, the tests were very similar in specificity and sensitivity, but in the case of lowly reactive sera the Richardson modification was much the easier to read.

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# SYNERGIC ACTION OF PENICILLIN AND SULPHATHIAZOLE IN GONORRHOEA

BY

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The control of venereal diseases in rural areas presents certain problems and difficulties not met with in the city. The County of Cornwall, with which this paper deals, has a scattered population of 322,500. No industrial areas exist, but there are some half dozen market towns and small seaports each with from ten to sixteen thousand inhabitants. Five clinics for the treatment of venereal diseases are established, but even so patients have to travel as much as thirty miles by indifferent bus and rail services to attend. Beds for the reception of venereal disease cases are reserved at the Royal Cornwall Infirmary, Truro, but as such accommodation is limited reliance has to be placed on efficient out-patient treatment at the clinics.

The present investigation of acute gonorrhoea was undertaken to find a treatment that could safely be employed on patients attending at once-weekly clinics and that also would give a high percentage of cures. The following three methods of treatment were investigated: (1) a single injection of 200,000 units of penicillin in oil beeswax, (2) sulphathiazole 25 g over five days, 5 g being given daily, (3) a single injection of 200,000 units of penicillin in oil-beeswax on the first day, together with sulphathiazole 20 g over four days, 5 g., being given daily.

In order to obtain results that were comparable in so small a number of cases, only fresh male urethral infections showing a positive culture and smear have been recorded. The three methods were used in rotation until twenty patients in each group had been treated. The results were then reviewed and subsequently all cases received treatment by the method that had given the best rate of cure in this preliminary trial. The penicillin preparation used was the calcium salt suspended in ethyl oleate containing 4 per cent w/w beeswax.

## Penicillin

The efficacy of multiple injections of penicillin in the treatment of gonorrhoea is now well established. The Report of the Health Division of U.N.R.R.A. (1946) states that, of 12,403 male cases of gonorrhoea, 94.2 per cent were cured after one course of penicillin treatment and a further 4 per cent following a second course. Laird and Fieldsend (1946), having established that 100,000 units of penicillin was the minimum satisfactory dose, carried out investigations to ascertain the optimum spacing of the injections. They concluded that five injections of 20,000 units given at two-hourly intervals gave the best result, the failure and relapse rate being only 1.5 per cent. Marshall (1945) using 100,000 units in doses of 20,000 units at three-hourly intervals, reports 84 per cent cured.

Reports on the use of a single injection of penicillin are as yet few. Allan (1946), reported good results in a series of cases treated with a single injection of 200,000 units in aqueous solution. Batchelor and others (1946) investigated the effects of oil-beeswax suspensions of penicillin and conclude that single injections of 200,000 units of such a preparation will cure 90.2 per cent. of cases in males, and that a second such injection will raise the percentage of cures to 95.8 per cent.

## Sulphonamides

Sulphonamides, first used for the treatment of gonorrhoea in 1937, proved of great value during the subsequent five years but their efficiency appears to have waned during the war years, possibly on account of the spread of sulphonamide-resistant strains of gonococci.

Campbell (1944), in an interesting account of gonorrhœa affecting British troops in North Africa and in the central Mediterranean area, states that sulphathiazole cured 70 to 75 per cent. of cases of acute gonorrhœa in North Africa, but that in Sicily and Italy less than 25 per cent responded to a course of 25 to 30 g of sulphathiazole "As the campaign has progressed northwards in Italy and expert venereal diseases treatment units have moved forward, there has been a slight improvement in the picture, but considerably less than 50 per cent of acute gonorrhœa cases respond to an initial course of 25 to 30 g of sulphathiazole, and relapses are common"

#### Penicillin and Sulphathiazole

Little work has as yet been published on the synergic action of penicillin and sulphathiazole against the gonococcus. In a paper on the treatment of sulphonamide-resistant cases of gonorrhœa, Lees (1946) writes "A small series of cases were treated with sulphathiazole, 5 g a day for five days and 30,000 units of penicillin on the fifth day. The results were not good, and we could not confirm the published reports that there was a marked synergic effect and that 100 per cent cures could thus be achieved quickly. It was considered that such schemes of treatment were unlikely to have much further value, and the experiment was not pursued". Oard and others (1944) have published the results of a trial of combined sulphathiazole and penicillin treatment. They gave 8 g of sulphathiazole on the first

day and a further 4 g on the second day, also 50,000 units of penicillin were injected on the first day of treatment at the rate of 10,000 every three hours. In a series of 232 cases they record 95 per cent cures.

#### Results

Results obtained in the preliminary trial of twenty cases in each group are shown in the Table.

In view of the excellent results obtained by the combined action of penicillin and sulphathiazole, all subsequent cases were treated by this method. A series of fifty cases has now been completed, all have responded to an initial course, and no relapses have occurred during six months' surveillance. Tests of cure were carried out after one week, one month, three months, and six months, the first three tests included an examination of the urine by the two-glass method, together with urethral and prostatic smears and cultures. Blood for Wassermann reaction was taken at three months, and six months.

#### Discussion

The series of cases under review is necessarily small, but the clinical findings reported strongly suggest that penicillin and sulphathiazole exert a synergic action on the gonococcus. That such action exists against *B. typhosus*, has already been demonstrated in the laboratory by Bigger (1946) and clinically by Comerford and others (1946).

TABLE

Therapy	Penicillin 200,000 units	Sulphathiazole 25 g	Penicillin 200 000 units and sulphathiazole 20 g
Number of cases of acute gonorrhœa	20	20	20
Average number of days after onset of symptoms before commencement of treatment	7.4	5.0	5.5
Number of cases clinically cured at end of treatment	16	13	20
Number of cases requiring further treatment	4	7	0
Percentage of cases cured by one course of treatment (surveillance 6 months)	80	65	100

I have endeavoured to obtain laboratory confirmation of synergic action of the two drugs against the gonococcus, but I found it impossible to isolate a pure strain of gonococcus sufficiently virile to give trustworthy results

#### Summary

A series of sixty cases of acute gonorrhœa in males have been treated by (a) single injection of penicillin in oil-beeswax (200,000 units), (b) 25 g sulphathiazole over five days, or (c) single injections of penicillin in oil-beeswax (200,000 units) plus 20 g. sulphathiazole. The results obtained in groups (a) and (b) were in agreement with the consensus of opinion in the literature. The treatment by the combination of penicillin and sulphathiazole gave excellent clinical results, over fifty cases

have now been treated, with 100 per cent cures. All cases in this series have now completed six months surveillance, there have been no relapses.

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# A CASE OF TRANSFUSION SYPHILIS

BY

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The accidental transmission of syphilis as the result of blood transfusion is properly regarded as a medical catastrophe. It is, however, conceivable that under certain conditions the risk might be considered justifiable if the immediate aim was the preservation of life. The case shortly to be described may be regarded as falling within this category.

Rein and others (1938) estimated 68 cases in the literature, but Stokes (1944) asserts that "the reported incidence of transfusion syphilis is in ludicrous contrast to a reasonable estimate of its frequency," and suggests that reluctance to publish cases may for ever cloak its actual incidence.

## Case History

A European male, aged 34, intelligent, co-operative, and of good physique, while resident in the tropics was involved in a fracas during which he was struck heavily on the nose. One week later he developed a profuse epistaxis, and his nose was packed in hospital. Despite this the hæmorrhage continued to a stage of extreme exsanguination. Two European volunteers were called for, and blood from each was transfused into the patient after cross-matching. Preliminary Kahn tests were not done on the donors. The patient's condition improved rapidly and he was able to leave hospital.

Six weeks later he began to experience violent headaches and pain in the left hypochondrium. About 10 days after the first onset of symptoms he was readmitted to hospital complaining of fever, headache, pain in the left hypochondrium, generalized pains in the bones and slight sore throat. Immediately on admission blood films showed the presence of malignant tertian malarial parasites, and a course of mepacrine was therefore started, with the result that some symptomatic relief was obtained although the patient remained febrile. Radiographs of chest and sinuses were normal. Examination of the cerebrospinal fluid showed 7 cells per cmm, protein, 20 mg per 100 ccm, Kahn test negative. White blood cells were 6,000 per cmm, and the differential

count was normal. The Widal and Weil-Felix tests were negative.

Six days after admission a faint maculo-papular rash appeared, mainly situated on the trunk, and a blood Kahn test was reported "positive". Three days later a second Kahn test was reported as + + +, the fever persisted, and the rash grew more marked. There were no penile or other suspicious sores, and no mucous lesions. Five days later a provocative injection of neoarsphenamine (0.1 g) was given, and on the following day the rash was seen to be still more pronounced, while the Kahn was reported as + + + +. A standard course of therapy with neoarsphenamine and bismuth was then started. In 6 days the rash had disappeared and the patient was symptom-free and fit to leave hospital.

## Discussion

Unfortunately technical and geographical difficulties prevented the performance of the Wassermann reaction in addition to and as a check on the Kahn tests, and in consequence caution had to be observed in interpreting the serological findings in view of the possibility of false positives due to the proven coincident malarial infection. However, it was ultimately considered that the diagnosis of early syphilis was established beyond reasonable doubt on the basis of the typical rash, the repeatedly strongly positive blood test, and the immediate clinical response to specific treatment.

Before blood transfusion was accepted as the undoubted mode of infection, however, the personal and family history were closely investigated, and here it may be stated that the patient appeared on several different occasions and to several independent medical observers to be a reliable witness. He had no previous history of venereal disease, nor any previous penile, genital, or labial sores. He was married, and had 4 children, his wife and the children were healthy. He stated that his last sexual contact was with his wife,

and that it had occurred 16 months previously, before his departure overseas

After the diagnosis had been established, attempts were made to trace and examine the donors. One was found to be clinically and serologically negative, but the other had left the area. Subsequently this second donor was traced and was examined at another hospital, whence information was later forthcoming that he was found to be a sero-positive latent syphilitic (Kahn ++)

#### Summary and Conclusions

1. A case of early syphilis with coincident malaria is described, in which the diagnosis was based on the presence of a typical maculopapular rash, a strongly positive blood Kahn (the test being repeated 4 times), aggravation of the rash, and intensification of the degree of positivity of the Kahn test after provocative neoarsphenamine, and finally clinical improvement and symptomatic relief following the institution of anti-syphilitic therapy.

2. Furthermore, it is believed that the disease was acquired as the result of blood transfusion, because the patient denied the possibility of exposure during the preceding 16 months, his personal and family history were entirely negative, there were no signs of previous genital or other suspicious scarring, the time interval between the transfusion and the onset of symptoms was suggestive (6 weeks),

and one of the two blood donors was found on subsequent examination to have a blood Kahn of ++

3. Consideration of this case serves to emphasize the fact that, before any transfusion in which fresh blood is to be used, the following procedures should be carried out on every donor: (a) complete physical examination of oral mucosæ, trunk, anus, and genitalia, (b) Kahn test or slide agglutination test (where facilities exist), (c) thick blood film for malarial parasites (in malarious areas).

4. Should it ever become vital to employ the blood of an untested donor in an acute emergency, 10 mg of neoarsphenamine should be added to each 100 c cm. of citrated blood as a safeguard, as recommended by Kast and others (1939). Alternatively, mapharside (10 mg per 500 c cm.) may be used (Eichenlaub and others, 1941).

I wish to thank the Director-General Army Medical Services for permission to publish this report and Lt-Col R. R. Willcox, R.A.M.C. for much helpful advice.

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# RELIEF OF LIGHTNING PAINS IN TABES DORSALIS

BY

W FOWLER

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The immediate relief of lightning pains in tabetics remains a problem. Though sedatives are still the commonest drugs prescribed, medical measures such as administration of vitamin B<sub>1</sub>, ephedrine, adrenaline, and insulin have been suggested on supposed aetiological grounds, but have failed to meet with general approval. Surgical procedures, such as epidural injections, division of the nerve roots, and cordotomy, have also been tried with varying degrees of success. One year ago, it was thought that lightning pain might be relieved by anaesthetizing the skin area where the pain was felt, in the same way as the referred shoulder-tip pain in perforated peptic ulcer can be abolished by infiltrating the skin over the shoulder-tip with procaine hydrochloride. In 1936 Alajouanine and others, working on the assumption that lightning pains were due to peripheral stimuli, claimed that after 10 to 20 c cm of 2 per cent procaine hydrochloride were infiltrated into "trigger zones" in the skin, the pains disappeared.

## Report on Eight Tabetic Patients

The following is a report on eight tabetic patients who suffered from paroxysms of lightning pains, treated by infiltrating the affected skin areas with local anaesthetic. The patients complained of pain in the following situations: (1) on the dorsum of the right foot, (2) in the right heel, (3) over the centre of both tibiae anteriorly, (4) commencing in the middle third of both thighs posteriorly and shooting down the limbs, (5) the girdle, at the level of the epigastrium, (6) around the right side of the chest in the mid-dorsal region, (7) multiple over the middle third of the outer aspect of the left foot, (8) commencing in both inguinal regions and shooting down the thighs.

In each case, the paroxysms lasted between two and seven days and appeared at intervals of three to seven weeks.

## ANAESTHESIA

At first 2 per cent "novocain" was used, 2 to 4 c cm being required. Later it was found that an oily solution gave better results, and therefore "proctocaine" was substituted, 1 to 2 c cm being used. The following technique was adopted:

(a) Where the pain struck at a fixed point, as in Cases 2 and 3, the area of skin involved was infiltrated with anaesthetic.

(b) Where the pain travelled from a constant point, as in Cases 4 and 8, the skin was infiltrated as close as possible to that point.

(c) In the case of girdle pain it was found that satisfactory results were obtained by infiltrating the skin across the path of the pain on both sides of the trunk.

(d) Where the pains were diffuse on the foot, as in Cases 1 and 7, the affected area was blocked by infiltrating around the ankle as far as was necessary.

## Results

Both "novocain" and "proctocaine" gave immediate and dramatic relief from the paroxysm. Following "novocain" injection the pain returned after one to four hours, with "proctocaine," however, it was relieved for at least two to four days. In five of the cases one injection of "proctocaine" abolished the paroxysm, while in three cases two injections were required, in one case after two days and in the other two cases after four days.

In seven of the patients, in addition to the immediate relief experienced, the interval between paroxysms has lengthened and the severity of the paroxysms has diminished. In one instance, Case 5, the paroxysms, although relieved by the anaesthetic, have not diminished in their severity or frequency of recurrence.

This method of treatment has the following advantages: (1) it is easily performed, (2) the

patient is immediately relieved, (3) he does not need sedatives, (4) he can carry on his work

and at work until cure is effected by anti-syphilitic treatment

I am indebted to Dr Robert Lees for his interest and help

### Summary

A method of relieving the lightning pains of tabes dorsalis by local anæsthesia is described, whereby the patient can be kept free from pain

### REFERENCE

Alajouanine T, Thurel R, Brunelli, A. (1936)  
*Rev Neurol* 65, 60

## BOOK REVIEW

### THE GIRLS THEY LEFT BEHIND

By Grethe Hartmann

(Ejnar Munksgaard, Copenhagen 1946 Pp 207  
26 tables and graphs Price D cr 12—English price 15s)

Psychological studies in prostitution, such as those of Flexner and of Kemp, were made at a time when the chief instrument of investigation was the intelligence test, and their conclusion that prostitutes were drawn from the lower grade mentalities is now familiar. Recently further studies have been undertaken, using the newer methods of psychopathology and aimed not at the investigation of the hardened prostitute but at evaluation of the personality trends in what Glover calls the 'larval prostitute'. This book, in spite of its faintly ridiculous title, is another contribution to such studies and the subject matter consists of girls and women who were found to be sex contacts of German troops during their occupation of Denmark in the recent war. The author emphasizes that in most cases the women concerned were not of the hardened prostitute type, and in fact are better described as 'half prostitutes'.

The difficulty which faces the non-psychiatrist in making an appreciation of all these studies is chiefly that of avoiding the suspicion that, in such a highly subjective technique as psychiatric investigation, the research workers are not infrequently led into finding what they set out to find, in other words reading into their results the hypotheses with which they started. It is, for example, a frequently expressed conclusion nowadays that 'the broken home' is of prime impor-

tance in causing juvenile delinquency, sexual maladjustment, divorce and the pursuit of multiple, often entirely casual, sexual relations which is often called sexual promiscuity. Does 'the broken home' or marked parental discord, however, inevitably lead to these abnormal behaviour patterns? If not, what factor or factors are responsible for the discrepancy? Does it not too often seem that the alleged and fashionably pilloried sins of the parents are used by the young and those interested in the young as a convenient and facile excuse for absence of self-discipline? Or does all the ingenuity of the psychiatrist serve but to reiterate in modern jargon the old refrain 'there's no place like home'?

Altogether Dr Hartmann investigated the behaviour patterns and family backgrounds of two hundred and twenty seven girls and the detailed case histories take up about three-fifths of the book. Dealing with the incidence of venereal disease amongst the general population of Denmark, the author gives some interesting figures of the relatively enormous rise in venereal disease incidence during and after the German occupation. Some graphs are also given showing comparisons between Denmark and Sweden, which latter country of course was not occupied by Germany. In both countries there was a rise in the incidence of gonorrhœa and syphilis—much greater however, in Denmark—and in both countries the increase in the incidence of syphilis was much greater proportionally than that of gonorrhœa.

This book is a useful contribution to the relatively few epidemiological and socio-psychological studies of the venereal diseases F.R.C.

# ABSTRACTS

(The abstracts are divided into the following sections syphilis (general, therapeutic, pathology), gonorrhœa (general, therapeutic, pathology), other venereal disease conditions, public health After each subsection of abstracts follows a list of articles that have been noted but not abstracted All subsections will not necessarily be represented in each issue)

## SYPHILIS (GENERAL)

**Diagnosis of Hepatic Syphilis by Pneumoperitoneum** (Diagnostic par le pneumopéritoine d'un foie ficelé syphilitique Aspect radiologique et laparoscopique) BELBENOIT, S., and LOY, J (1946) *Bull Soc méd Hôp Paris*, 62, 393

The authors describe the use of pneumoperitoneum in the case of a 14-year-old girl who was suffering from ascites and who had an evening pyrexia of about 100.4° F. Mantoux tests and radiological examinations of the chest were negative and there was no wasting. A pleuroscope was inserted, after fluid withdrawal and air replacement, through a small incision in the left iliac fossa. The spleen appeared normal. The pelvis contained a little fluid, but there was no evidence of tuberculous peritonitis. A radiological examination was made after withdrawal of the instrument, and enough air still remained to show the irregular outline of the superior border of the liver. Pneumoperitoneum was performed, and the x-ray picture showed the liver to be a mass of rounded projections and deep furrows. An enlarged spleen was similarly outlined.

The endoscope was again inserted, 11 days after the first examination, at a point 4 fingerbreadths to the right of the umbilicus. The under surface of the pathological liver, with its projections and crevices, could be seen, and also varicose veins on the parietal peritoneum, analogous to the caput medusæ of the anterior abdominal wall. A Wassermann reaction was strongly positive, as was that of the blood of the patient's mother. A diagnosis of hepatic gummatosis due to congenital syphilis was made.

Between Oct 4, 1945, and Feb 20, 1946, 242 g of potassium iodide was given by mouth, 10 injections of enesol (mercuric salicylarsenate), 9 injections of acetylarsan (acetarsol sodium), and 12 injections of mercury were also administered. The patient was by now improved and ambulant. The ascites and pyrexia subsided. A further endoscopy was done, but no definite improvement in the appearance of the surface of the liver was noted.

R R Willcox

**A Case of Myopia and Hereditary Syphilis** (Myopie et heredo-syphilis) HERVOUET, F (1946) *Paris méd*, 36, 441

## SYPHILIS (THERAPEUTIC)

**Temperature Regulation Changes in Congenital Syphilis** (Le alterazioni della termoregolazione nella sifilide congenita) BOLLETTINO, A (1946) *Pediat Med prat*, 19-21, 331

A case of "essential luetic fever" in a 3-months-old infant with congenital syphilis is described. According to Milian, pyrexia is present in 25% of cases of congenital syphilis, and the affected infants frequently show a marked thermic lability. Where secondary infection is absent the temperature does not usually rise above 38° C, apart from the acute initial stage of the variety called "septic lues". The fever in congenital syphilis characteristically precedes the manifestations of organic foci—for instance, those of osteochondritis, arthritis, hepatomegaly and splenomegaly, and lymph-node enlargement. The condition of the patient is influenced more by the nature of the organic lesion than by the temperature. Another frequent sign of congenital syphilis in the infant is an abnormally low temperature, or a disorder of the temperature regulation in which hyperthermia and hypothermia alternate. The latter is often refractory to mercury and responds only to arsphenamine preparations. In "essential syphilitic fever" there are no other signs of disease.

In the case described the parents were undergoing antisyphilitic treatment. When the child was 2 months old rises of temperature up to 38.5° C were first noticed. As a lung infection was suspected, a sulphonamide preparation was prescribed. The temperature curve, however, assumed the character of a continuous fever, between 38.5° and 39.9° C. The nutritional condition (after a febrile phase of 1½ months) was only slightly affected, the skin was pale and dry, and the muscles hypotonic and hypotrophic. There was a diffuse distribution of small swollen lymph nodes, while the liver and spleen were enlarged with sharp margins and of hard consistency. The urine contained albumin ++ and some casts. Blood examination showed anæmia, lymphocytosis, and eosinophilia. The Wassermann test was positive. Acute or subacute infections of gastro-intestinal, pulmonary, or oral origin were excluded by the regular increase of weight, in spite of prolonged fever, in an artificially fed child. Typhoid fever was excluded by blood and serum examination, there was no sign of tuberculosis, the moderate monocytosis excluded

glandular fever, and the infant did not show the other characteristics of this condition. X-ray examination showed no local syphilitic changes in the bones.

During the first 2 weeks treatment consisted of mercury inunctions and a sulphonamide preparation orally, protein shock therapy was also used [names of preparations are not given]. In this period the condition of the kidneys improved rapidly (albumin and casts disappeared from the urine) and the size of the liver and spleen diminished progressively. The fever remained unaltered, but in spite of this the infant showed a regular increase in weight and improvement of nutrition in the third week. Treatment with neoarsphenamine injections was started while the mercury inunctions were continued. With the introduction of this treatment the fever terminated by crisis and the blood count became normal. The negative response to sulphonamide and protein therapy, the partial effect of the mercury treatment, and the striking change brought about by the arsenical injections are taken as proof of the essential syphilitic nature of the fever.

This essential syphilitic fever is regarded as an expression of syphilitic toxæmia together with either an organic hypersensitivity or a particularly virulent infection in an individual with low immunity.

*Hilde Eisner*

**Bismuth Treatment of Early Syphilis** SOCIÉTÉ FRANÇAISE DE DERMATOLOGIE ET DE SYPHILIGRAPHIE (1946) *Ann Derm Syph*, 6, 279

In the last few years certain French syphilologists have been using bismuth almost exclusively in the treatment of early syphilis. The arsphenamines have been abandoned because of their toxicity.

Lortat-Jacob reports on 150 cases of early syphilis treated with bismuth alone. Negative reactions were obtained in 98% of the cases of primary serum positive syphilis (90) and in 84% of the cases of secondary syphilis (60). Burnier gives the following results in 800 cases treated by various methods: (a) with neoarsphenamine alone 66% of cases were serum-negative a month after the first course, (b) with neoarsphenamine and bismuth, 72% were serum negative after 1 course, and 82% after 2 courses, (c) with bismuth alone, 80% serum negative after 1 course of 12 injections, and 96% after 2 courses. There were no grave toxic effects in the cases treated with bismuth alone but 3 patients died during the period of survey while under treatment with arsenic, either alone or with bismuth. Fernet and Guibert report reversal of positive tests in 28% with one course of bismuth alone, and prefer mixed treatment for cases of early syphilis.

Gaté and Cuilleret treated 310 cases of early syphilis with bismuth alone and attained serum-negativity after 1 course in 48%, after 2 courses in 29%, after 3 courses in 10%, and after 4 courses in 3% of cases. In 63 cases treated with arsenic and bismuth blood tests were negative after 1 course in 42% and after 2 courses in 37%. They conclude that there is no advantage in respect of

serological response in using mixed treatment, and state that bismuth alone is sufficient treatment both for attack and for maintenance in most cases of early syphilis. Toxic effects and bismuth resistance are rare.

Garnier retained his confidence in the tervalent arsenicals which, he said when associated with bismuth, rapidly sterilized the lesions of early syphilis and gave the greatest chance of clinical cure.  
*James Marshall*

**Use of Penicillin in the Treatment of Syphilis in Pregnancy** COLE, H N, AYRES S BARR, J H., GENATIOS, T., HELD B., MURPHY W W., PRINTZ D R., and STRAUCH J (1946) *Arch Derm Syph Chicago*, 54, 255

Since October, 1943 730 patients with early syphilis have been treated with penicillin at the University and City Hospitals of Cleveland. The possible effects of alterations in the constitution and potency of commercial penicillin during this time have not been assessed. The routine clinical and pathological examinations are described. Lumbar punctures were made on all patients, and if the fluid was abnormal tests were repeated on discharge of the patients and thereafter if possible every 3 months. Serum tests for syphilis were made every 2 or 3 months after discharge. Acute surface lesions heal rapidly and may clear up in 1 to 3 weeks. Dark field examinations of open genital lesions usually become negative in 12 to 18 hours. The titre of positive serum tests may rise for a week or more after beginning treatment, and then gradually drop to negativity in from 4 to 12 weeks. Reactions to penicillin included local pain with certain batches, Herxheimer effects early in treatment, herpes labialis, urticaria and multi-form and nodose erythematosa.

The authors believe that syphilis in pregnancy is a suitable condition for the use of penicillin as they discovered no danger of complications or of damage to the child. Even with very small doses the child may be born free from syphilis but to avoid the possibility of relapse in the mother doses of 2,400,000 units or over must be used. Successful results as regards the child can be achieved even at the end of pregnancy. The necessity for the use of quantitative serum tests in a check up on the mother and child is stressed.

*James Marshall*

**Neurosyphilitic Patients Treated with Penicillin** Probable Herxheimer Reactions TUCKER H A., and ROBINSON R C V (1946) *J Amer med Ass*, 132, 281

The authors believe that it is important to record two examples of probable Herxheimer reaction during penicillin treatment of neurosyphilis. The first patient was a woman with dementia paralytica. Treatment comprised 50,000 Oxford units of sodium penicillin given intramuscularly in normal saline every 3 hours to a total of 10,000,000 units. After 30 hours the patient's rectal temperature had risen to 100.8° F and at 42 hours a prolonged series of clonic

convulsions began, affecting the right arm and leg and the right side of the face. Swallowing was impaired and plantar responses were extensor. In spite of anticonvulsant drugs the convulsions continued for 15 days, penicillin being given all the time. Eight days later the patient left hospital, and clinical improvement continued for the 6 months during which the patient was followed up.

The second patient had penicillin therapy similar to that used in Case 1. After 8 hours the patient had a rectal temperature of 102.6° F, which returned to normal spontaneously. Thirty hours from the beginning of the therapy he was found on the floor, moaning and throwing his body from side to side. There was vomiting, incontinence, disorientation, restlessness, and meningeal irritation, plantar responses were extensor. Lumbar puncture gave a clear, sterile fluid under normal pressure but the pleocytosis had increased to 277 cells per c mm, of which 52% were polymorphonuclear cells. The rectal temperature rose to 104.8° F. Sedation was required for 3 days, after which the patient recovered.

The authors believe that these reactions were probably examples of the Jarisch-Herxheimer phenomenon. They do not consider that the convulsions in their own patients were due to a direct irritative action on the nervous system since (a) only insignificant amounts of penicillin were demonstrated in the spinal fluid, and (b) the convulsions ceased although penicillin was continued throughout in full doses. The penicillin used contained penicillin G, F, and K in unknown proportions, K probably being the predominant fraction, and the authors speculate whether differences between the various penicillin fractions are concerned in the production of irritative reactions in the nervous system.

S M Laird

**Penicillin in the Treatment of Neurosyphilis. I. Asymptomatic Neurosyphilis.** MOORE, J E, and MOHR, C F (1946) *Amer J Syph*, 30, 405

Detailed results are presented of penicillin therapy in 48 patients with early and 43 with late asymptomatic neurosyphilis followed for an average period of 9 months after treatment. The authors' definition of asymptomatic neurosyphilis is "that form of syphilis in which neither symptoms nor abnormal clinical signs are present which direct attention to the nervous system, but in which the spinal fluid routinely examined is abnormal." The cases are subdivided into early and late asymptomatic neurosyphilis, the dividing line was arbitrarily chosen on the basis of duration of infection of less or more than 4 years. Treatment was by intramuscular injections of aqueous sodium penicillin, which were given every 3 hours day and night, the total amount of penicillin given varied from 0.06 to 6 mega units. None of the patients with early asymptomatic neurosyphilis developed any clinical evidence of neurosyphilis during the post-treatment observation period, which in no case was more than 18 months, and, as pointed

out by the authors, this period is too short to yield data of prognostic value.

The number of patients was considered to be too small to permit a detailed analysis of the results according to penicillin dosage, but the authors think there is no essential difference in the cerebrospinal fluid results in general in relation to dosage. It is recommended that for early asymptomatic neurosyphilis not less than 2.4 mega units of penicillin in 7½ days should be given, for late neurosyphilis, as well as for cases of early asymptomatic neurosyphilis with a parietic formula, the total should be not less than 4 mega units in 10 days.

V E Lloyd

**Treatment of Gummatous Hepatic Syphilis with Penicillin. Report of Two Cases.** TUCKER, H A, and DEXTER, D D (1946) *Arch intern Med*, 78, 313

Two patients with gummatous hepatic syphilis were treated with penicillin. The first was a negress, aged 49, who was emaciated and chronically ill, and her liver greatly enlarged and tender, several large nodules being felt on its anterior surface. The spleen was palpable. The patient showed evidence of osteo-periostitis of the right femur and patella, and a loud blowing systolic murmur and an accentuated aortic second sound were heard. Pyrexia ranging as high as 103.2° F was constant, and the Eagle test for syphilis gave a positive reaction. Penicillin was given (5,000 units intramuscularly 3-hourly for 64 injections in 8 days). The temperature became normal, the pain over the liver and in the knee diminished, and within a month the spleen could no longer be felt. Because of this excellent response a further course of penicillin was begun, 10,000 units being given 3-hourly for 60 injections in 7½ days to a total of 600,000 units, bringing the dosage of penicillin in the two courses to 920,000 units. The patient put on weight and was discharged from hospital. The size of the liver continued to decrease, until at the last examination, 686 days after starting treatment, its edge was felt only 3 cm below the costal margin. The Eagle reaction was still positive.

The second patient, a 15-year-old white girl, had an enlarged tender liver down to the umbilicus as well as a palpable spleen. A nodule was seen and felt on the anterior surface of the liver. Eagle and Wassermann tests were positive. Biopsy of the hepatic nodule revealed large areas of necrosis surrounded by fibrous tissue, occasional scattered solitary tubercles, and a slight infiltration of mononuclear cells. The pathologist reported "probable gumma of the liver." She was given 40,000 units of penicillin intramuscularly every 3 hours for 80 injections—a total of 3,200,000 units in 10 days. The temperature rose to 100.4° F 15 hours after the start of treatment, this being interpreted as a probable Herxheimer reaction. Her condition improved, until after 4 months the liver was practically normal in size. Though the Eagle reaction was still positive, the Wassermann was negative, the blood was normal and there was no clinical evidence of hepatic dysfunction.

[Although penicillin would appear to be an ideal therapeutic substance in hepatic syphilis, there would seem to be risk in giving so powerful a drug without preparatory bismuth treatment. In the first case a cardiac Herxheimer reaction was a possibility, especially in view of the raised pulse pressure and the accentuated aortic second sound.]

G L M McElligott

**Penicillin in the Treatment of Syphilis in Children**  
YAMPOLSKY, J, and HEYMAN A (1946) *J Amer med Ass*, 132, 368

The results are reported of treatment with penicillin in 54 congenital syphilitics and in 7 children with acquired primary and secondary syphilis. During 20 months the authors treated with penicillin alone 32 children with infantile congenital syphilis, 22 were watched for 12 to 20 months, 7 for 4 to 8 months, while the remaining 3 died from causes unconnected with the treatment. At first 40,000 to 50,000 units of sodium penicillin per kilo of body weight was given intramuscularly every 3 hours for a total of 60 doses in 7½ days, but when failures were observed the dosage was raised to 60,000 and 70,000 units. An immediate clinical response occurred in all patients. The serological tests became negative in 18 cases, decreased in titre in 5, but remained sero-resistant in 6. Harmless Herxheimer elevations of temperature occurred in 50% of cases, no other reactions were seen. Penicillin was effective in only 1 case of interstitial keratitis, 3 improved and 5 were unsatisfactory. No benefit resulted when penicillin was instilled locally. Three children with Clutton's joints (symmetrical hydrarthrosis) and 2 with juvenile general paralysis failed to respond clinically. In late congenital asymptomatic neurosyphilis the cell count and protein content of the cerebrospinal fluid were reduced rapidly in 6 patients, and became normal within 12 months in only 4 of these. The Wassermann reaction however, has remained positive in every case. In one severe case of eighth-nerve deafness no change was detected, but hearing was improved in a milder case. The lesions in the 7 cases of acquired syphilis healed promptly and the spirochaetes disappeared rapidly, but in only 2 did the serological reactions become positive.

This study suggests that infantile congenital syphilis and early neurosyphilis respond well, and that interstitial keratitis, Clutton's joints, eighth-nerve deafness, and juvenile general paralysis are refractory—that is to say, that only a poor response is to be expected in the late manifestations of the disease.

[General experience suggests that the doses of penicillin employed were too small, and that much better results would be obtained if the dosage is raised to at least 100,000 units per kilo of body weight, and if penicillin is combined with bismuth and arsenical therapy.]

T Annryl Davies

**Inadequate Dosage of Penicillin in the Treatment of Syphilis. Report of three Cases (Dosis insuficientes de penicilina. Comunicacion de tres casos)** BLADUELL, H A (1946) *Bol Asoc med P Rico*, 38 210

## SYPHILIS (PATHOLOGY)

**Value of Hoffmann's Lymph node Puncture in the Diagnosis of Early Syphilis (Der diagnostische Wert der Erich Hoffmannschen Lymphdrüsenpunktion bei frischer Syphilis)** WILDE H (1946) *Arzt Wschr*, 1, 93

Erich Hoffmann first demonstrated in 1905 that lymph node puncture is a valuable aid to the diagnosis of syphilis in its earliest stages. Positive results by this method may establish a diagnosis weeks before serum reactions become positive. *Treponema pallidum* can be found by lymph-node puncture in a very high percentage of cases of early syphilis—100% according to Photinos, over 90% according to Habermann and Mautelshagen. Specimens are collected in the following manner: After cleansing the skin a wide bore needle on a tight-fitting 10-ml syringe is plunged into the lymph-node substance. The lymph node is fixed between thumb and forefinger of the other hand and gently massaged while suction is applied continuously by the syringe and the needle is moved about. The needle is then withdrawn and its contents expressed on to a slide and prepared for dark-ground examination.

The author found *T. pallidum* by this method in 84 out of 100 cases of proved primary syphilis. In 34 cases a positive result was obtained at the first test: in 23 at the second, in 11 at the third, in 8 at the fourth, in 4 at the fifth, in 1 at the sixth, in 2 at the seventh, and in 1 at the eighth. *T. pallidum* was discovered in 49 of 78 cases with phumosis due to inflammatory conditions. Further investigation of the 29 negative cases, after dorsal slit, showed them to consist of 8 primary chancres, 12 soft sores and 9 non-specific ulcers. The method is useful when *T. pallidum* cannot be found in sores which have been treated locally with antiseptic. In secondary syphilis positive tests were obtained in this manner in 44 of 63 cases—a smaller percentage of positives than in the primary stage.

J Marshall

**Permeability of Blood-Spinal Fluid Barrier in Infants and in Normal and Syphilitic Adults.** KALZ, F, FRIEDMAN H, SCHENKER, A., and FISCHER, I (1946) *Arch Neurol Psychiat*, Chicago, 56, 55

The relative permeability of the blood-spinal fluid barrier in infants, normal adults, and syphilitic adults was investigated. Positive Wassermann reactions in the spinal fluid seldom occur without syphilitic involvement of the central nervous system, false positive reactions, however, have been found in patients with meningitis of bacterial or virus origin. The serum Wassermann reaction also being positive. The blood spinal fluid barrier is presumably impaired in such cases by the meningeal inflammation. The spinal fluid of 16 new born infants with syphilis was examined. Normal results were found in 4, evidence of syphilitic involvement of the central nervous system in 4, and moderately positive Wassermann reactions with normal cell counts, protein values, and colloidal gold curves in 8. In the last group the Wassermann serum reactions were positive in

dilutions of from 100 to 300, the spinal fluids giving positive reactions with 1 and 0.6 ml and negative reactions with 0.4 ml, results suggestive of a passive transfer of reagin from the blood into the spinal fluid. The 4 infants with neurosyphilis, treated with sulpharsphenamine in the usual dosage, showed completely normal spinal fluids within a short period. This quick reversal of the spinal fluid to normal in very young children may be assumed to be due to an undeveloped barrier between blood and spinal fluid. Experimentally, a high permeability of the barrier has been found in new-born animals, gradually decreasing with the growth of the animal.

In the present investigation 4 groups of patients were tested, normal adults, adults with untreated neurosyphilis, adults with neurosyphilis who had received at least 1 year of treatment with fever therapy and/or pentavalent arsenicals, and non-syphilitic infants under 18 months of age. Walter's bromide test, which demonstrates normal, increased, or decreased permeability of the blood-spinal fluid barrier, was used, adapted to photo-electric readings. It was found that the values for infants were significantly lower than those for normal adults and were comparable to those given by adults with neurosyphilis. It is considered that, in the absence of other evidence, positive Wassermann reactions of the cerebrospinal fluid of syphilitic infants should not be taken as proof of neurosyphilis.

M Mackenzie

#### Preservation of Virulence of *Treponema pallidum*

Some Additional Laboratory Methods STRATTON, E K (1946) *Arch Derm Syph*, Chicago, 54, 25

The author describes experiments which resulted in mouse-to-mouse transfer of *T. pallidum* without the use of an intervening host, though rabbit inoculations were performed as an indicator of success. Twelve white mice were inoculated subcutaneously with chancre grafts from a rabbit's testicle (Nichols' strain). After a lapse of 6 months 6 of the mice were killed and the lymph nodes, spleens, and brains, were separately pooled and emulsified. None of these 3 pooled specimens showed *T. pallidum* on dark-ground examination, though all produced a specific orchitis after inoculation into a rabbit's testicle. Twelve more mice were then injected with each of the 3 emulsions, and, after a further 6 months, 6 from each group were killed and similar pooled emulsions prepared from the spleens, brains, and lymph nodes. On testing the virulence of these against rabbits, negative results were obtained with all specimens from those mice which had received emulsions of spleen and brain, and no further passage was found possible. Positive results were, however, obtained with all 3 emulsions prepared from the mice which had received the injection of pooled lymph nodes. The second positive lymph-node emulsion was injected into 12 more mice, and after 6 months the 3 emulsions were again prepared and tested against the rabbit as before. The pooled brain and spleen emulsions were avirulent, but the one prepared from lymph nodes produced a specific orchitis in a rabbit. Further similar passage was obtained with this lymph-node

emulsion into yet another series of mice, in which again only the lymph nodes were proved to be virulent.

Another series of experiments was conducted to assess the behaviour of infected syphilitic tissue in the frozen state. Two specimens each of rabbit lymph nodes, mouse brain, mouse lymph nodes, and mouse spleen were emulsified. No *T. pallidum* was detected in any of the emulsions though all would produce a specific orchitis in a rabbit. The emulsions were frozen and kept in a refrigerator at  $-78^{\circ}\text{C}$  for 1 year, when, after thawing in a water bath at  $37^{\circ}\text{C}$ , they were injected into rabbits' testicles. All preparations of rabbit lymph node and mouse brain gave negative results. Both specimens of mouse lymph node caused small indurated nodules in which an occasional *T. pallidum* was found, while both mouse spleens produced voluminous orchitic swellings in which the organism was easily found 60 days after inoculation.

R R Willcox

#### A Simple Method for Performing a Wassermann Test on Anticomplementary Serum TARAN, A (1946) *J Lab clin Med*, 31, 1037

Anticomplementary reactions in the Wassermann test are unsatisfactory because no result can be reported and it is necessary to obtain a second specimen of blood. An anticomplementary reaction is due to the fact that the patient's serum alone has the ability to fix complement, the author therefore tried the effect of saturating with neat complement the serum to be tested and then inactivating the mixture to destroy any excess of complement. The serum was then tested in the ordinary way and found to react normally. This technique was applied to 200 anticomplementary sera over a period of 15 months, known positive and negative sera and fresh specimens from the patients who provided the original anticomplementary sera being included as controls.

The majority of anticomplementary sera were positive. It was found that the addition of complement, as described, to known negative and positive sera used as controls did not affect the reactions. This method is not recommended in the case of sera which show much haemolysis or heavy contamination, in such cases fresh specimens should be obtained.

[A much larger number of specimens should be tested before this technique is adopted as a routine, since weakly positive sera might be affected by the mere dilution, it is known also that the behaviour of certain sera is different when diluted with a known negative serum from what it is when diluted with saline.]

T E Osmond

#### Syphilitic Amyotrophy Clinical-pathological Report of a Case Complicating Tabes Dorsalis LICHTENSTEIN, B W, and LUHAN, J A (1946) *J Neuropath*, 5, 321

Liver Function Tests in Neurosyphilitic Patients with Induced Vivax Malaria of Pacific and Mediterranean Origin LIPPINCOTT, S W, MARBLE, A, ELLERBROOK, L D, HESSELBROCK, W B, ENGSTROM, W W, and GORDON, H H (1946) *J Lab clin Med*, 31, 991

## GONORRHOEA (THERAPEUTIC)

Oral Penicillin in Gonorrhoea BUSHBY, S R M., and HARKNESS A. H (1946) *Lancet* 2, 783

As a preliminary to the use of penicillin by the mouth in gonorrhoea, determinations were made of the amounts in the blood after the ingestion of tablets of calcium penicillin. After a single dose of 40,000 or 60,000 units, together with sodium citrate, taken an hour after breakfast, penicillin appeared in the blood within 30 minutes reached a peak at about 1½ hours but was not detected at 5½ hours. When the tablets were coated with a multilayer enteric protective, penicillin did not appear in the blood until after 2½ hours, and was not detected at 5½ hours.

After preliminary trials had shown that periods of treatment up to 12 hours were too short, 62 cases of gonorrhoea in men were treated with 6 doses of calcium penicillin, 40,000 units, and 1 g. of sodium citrate 3 hourly. Fluids were restricted to 1½ pints (852.37 ml.) during treatment. Serum penicillin levels were determined in 53 cases and showed considerable variations. The urethral discharge often became more profuse in the first few hours of treatment, and then became progressively less in amount and muco-purulent or mucoid in character 2 to 5 days later. The urine contained a few mucous threads up to the end of a week. Symptoms such as dysuria disappeared. Bacterial examination of smears every 2 hours showed normal gonococci to have been present up to 2 hours and in some cases up to 4 hours. Giant forms were seen up to the sixth hour after treatment. Cultures taken 2-hourly rarely grew gonococci after smears had become negative. Most of the cases were under observation for 6 months. The final assessment showed 4 failures and 2 reinfections. Two relapses had followed the use of the earlier trial scheme of treatment over 12 hours. Only 2 failures were encountered in the series of 62 cases receiving 6 doses of 40,000 units 3-hourly over 15 hours. One case developed acute epididymitis which was thought to be of non-specific origin.

A recommendation of this method of treatment for gonorrhoea in men is coupled with a warning of the importance of regular dosage, of the restriction of fluids, and of giving each patient short and concise instructions.

V E Lloyd

The Adequate Treatment of Gonorrhoea. HELLER, J R (1946) *J vener Dis Inform*, 27, 225

Data are given from the most recent U.S. Public Health Service investigations on the use of penicillin in gonorrhoea by short treatment schedules. Certain previous studies of the same Service are also reviewed, and the possibility is indicated of reducing the incidence of gonorrhoea by the use of these short schedules in private practice. Two treatment schedules were studied: one that could be completed in 2 hours and one which required 3. A study was made of 396 patients in all of whom diagnosis was confirmed by a positive culture. 83% were observed for 10 days or longer, the

remainder for 6 to 9 days. The 2 hour schedule was adopted for 255 patients, who received 200 000 units of sodium penicillin dissolved in 6 ml. of water in 3 intramuscular injections of 50,000, 50 000, and 100 000 units respectively, at hourly intervals. The 3-hour schedule was given to 141 patients, and consisted of 40,000 40,000 40,000, and 80,000 units intramuscularly. Among the patients observed for 10 days or longer, 94% were cured by the 2 hour schedule and 96% by the 3-hour schedule. Of the patients from whom a positive culture was obtained before treatment 92% were classified as cured after treatment.

[The period of observation in this investigation must be considered to be very short.]

T Anwyl-Davies

Oral Penicillin in the Treatment of Neisserian Infections SEAGER L D, SHOEMAKER, W G, MULHOLLAND S, MILLER, R E., WELLS G R., and BARNES K B (1946) *J Urol*, 56, 594

The authors discuss methods of administering penicillin by mouth so as to minimize the destructive effect of the acid of the gastric juice on the drug. Their conclusions are summarized as follows. Penicillin is effective in the treatment of gonorrhoea when given by mouth. Blood level and clinical cure proved that enteric coating and the incorporation of the drug in a vehicle such as lanolin sesame or cocoa butter permit satisfactory absorption. By this method, clinical cure in 15 cases was obtained, the percentage comparing favourably with other methods of administration. Three to six times the intramuscular dose was required. Sulphonamide-resistant cases of gonorrhoea were more easily cured by penicillin than were fresh infections.

T W Munpriss

A Case of Acute Generalized Gonococcal Peritonitis (A propos d'un cas de péritonite aiguë généralisée à gonocoques) GUENIN R. (1946) *Gynaecologia Basel* 122, 224

The literature on generalized gonococcal peritonitis is reviewed and one illustrative case is described.

## GONORRHOEA (PATHOLOGY)

The Role of Lens Substance in Experimental Gonorrhoeal Iritis. DRELL, M J, BOHNHOFF M., and MILLER, C. P (1946) *Amer J Ophthal*, 29, 1263

Experiments were undertaken as an extension of studies on experimental gonorrhoeal iritis in rabbits [Their practical relevance to clinical iritis in man is problematical, gonorrhoeal iritis occurs most commonly without lens trauma. As the authors point out, postcataract inflammation from whatever cause, is always more severe in cases where much soft lens matter is present. The work does suggest that in such cases the effect of the soft matter lies more in its facilitating the multiplication of bacteria than in an inherent toxic effect or immunological reaction.]

A J B Goldsmith



## OTHER VENEREAL DISEASE CONDITIONS

**Thrombo-angitis, Phlebitis and Lymphangitis of the Spermatoc Cord in Relation to Lymphogranuloma Venereum** COUTTS, W E, and ZALAZAR, R V (1946) *Urol cutan Rev*, 50, 526

The authors assign their cases to 3 clinical groups (1) inflammation of vascular elements of the cord only, (2) the same, with inflammation of the caput epididymidis, (3) both these, together with inflammation of the vas and of the rest of the epididymis. The third group is the largest. Vas and vessels are enlarged and tender, and there is usually pan-epididymitis. There is purplish oedema of the inguino-scrotal-fold and scrotum, tortuous scrotal veins are seen, and the deep iliac lymph nodes are enlarged and tender. Acute or subacute gonorrhoea is a usual concomitant. In the differential diagnosis of the first group of cases from torsion of the spermatic cord, enlargement and tenderness of the deep iliac lymph nodes are important.

Since the advent of penicillin therapy for gonorrhoea the authors have observed an increase in the number of cases of cord and epididymal involvement. Their explanation of this increase is that sulphonamides in gonorrhoea acts both on viral and coccal infections, so that testicular complications almost disappeared. Penicillin, on the other hand, cures gonorrhoea, but does not attack the lymphogranuloma venereum virus, which may originate genital complications. These are cured on reversion to sulphonamide therapy. The authors conclude that this virus may be responsible for thrombo-angitis, phlebitis, and lymphangitis of the spermatic cord, and that in cases of gonorrhoeal epididymitis with severe inflammation of the vascular elements of the spermatic cord an associated lymphogranuloma venereum infection must always be suspected, and search made for inflamed deep iliac nodes.

Alex E Roche

**Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group. I Effect of Penicillin and Sulfadiazine on Ten Strains in Chick Embryos** MEIKLEJOHN, G, WAGNER, J C, and BEVERIDGE, G W (1946) *J Immunol*, 54, 1

Several members of the psittacosis-lymphogranuloma-venereum group of viruses have been shown to be susceptible to the action of the sulphonamide drugs and penicillin. Two of the group—a virus (Borg) isolated from an outbreak of pneumonitis in Louisiana and the S-F strain isolated from an outbreak of pneumonitis in San Francisco, both of which are extremely virulent for man—have not previously been studied with regard to susceptibility to sulphonamides and to penicillin. Comparative tests were made on the 6BC and the Gleason strains of psittacosis, the P207 strain of pigeon ornithosis, the Borg strain, S-F strain, the Cal 10 strain of meningo-pneumonitis, feline pneumonitis, the Greb strain of mouse pneumonitis, the 12XN strain of hamster pneumonitis, and a strain of lymphogranuloma venereum. The dose of virus used was, when

possible, large enough to kill all untreated embryos between the fifth and eighth days after inoculation.

Sulphadiazine in relatively small doses—0.1 to 2.5 mg—showed therapeutic effects against the two strains of psittacosis, the virus of mouse pneumonitis, the 12XN strain of hamster pneumonitis, and a strain of lymphogranuloma venereum. It had little, if any, effect against the other 5 strains of virus, even when dosage was increased to the limit of toxicity (40 mg). All 10 strains were susceptible to penicillin. Relatively large amounts—1,250 units—of penicillin were required with the classical psittacosis strains and the two virulent human pneumonitis strains—Borg and S-F. Lymphogranuloma venereum, which is not inhibited by penicillin in the mouse, was inhibited by less than 50 units. It is of interest to note that eggs treated with either drug continued to harbour the virus.

F O MacCallum

**Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group. II Effect of Penicillin and Sulfadiazine on Seven Strains in Mice** WISEMAN, R W, MEIKLEJOHN, G, LACKMAN, D B, WAGNER, J C, and BEVERIDGE, G W (1946) *J Immunol*, 54, 9

A number of the strains described in the previous experiments (see above abstract, *J Immunol*, 54, 1) had not been tested for their susceptibility to drug treatment by penicillin or sulphadiazine when infecting mice, and tests on seven of them are described here.

Penicillin had a therapeutic effect in mice infected with psittacosis, Borg human pneumonitis, Cal 10 meningo-pneumonitis, pigeon ornithosis, and mouse pneumonitis when it was given by the subcutaneous route, but not when the oral route was used. This latter failure was probably due to insufficient ingestion or absorption of the drug. Sulphadiazine was effective against only the two strains of psittacosis, the mouse pneumonitis of Nigg and the hamster pneumonitis. The results obtained in mice agreed in each instance with those in chick embryos, although the blood levels in mice, particularly with penicillin, were far lower than those in chick-embryo fluids. These results indicate that effective blood levels may differ greatly in different hosts.

F O MacCallum

**Isolation of the Virus of Lymphogranuloma Venereum from Twenty-eight Patients, Relative Value of the Use of Chick Embryos and Mice** WALL, M J (1946) *J Immunol*, 54, 59

The specimens tested for the presence of virus were biopsy material or aspirations from buboes. Infection in eggs of the first passage, after yolk-sac inoculation, was usually not readily apparent, and elementary bodies were difficult to find. Consequently "blind" passages were often done 7 to 12 days after inoculation. By the second or third passage of positive material, some of the embryos became sluggish and elementary bodies were more easily found. However, numerous bodies did not appear until the fourth or fifth passage, when most of the embryos became moribund in 3 to 4 days.

Young white Swiss mice were used and injected intracerebrally. Those which became sick did so in 3 to 7 days, and if any of a group was ill, usually all were. The virus was isolated from 28 of 33 patients thought to have lymphogranuloma venereum. Virus was isolated altogether 41 times—38 from bubo aspirations, 2 from excised lymph nodes, and 1 from a penile lesion. In mice, virus was isolated from 39 out of 40 specimens tested, mice not being available for one sample. In the yolk sac the virus was recovered from 32 of the 41 samples. Strains isolated in only one host were readily adapted to growth in the other. The principal fault of the yolk-sac method was the susceptibility of the embryo to bacteria, since 6 of the failures of this method were attributed to bacteria (usually diphtheroids or *Staphylococcus albus*) which did not interfere with the virus isolations in mice. Because of the earlier signs of infection in mice, diagnosis of the virus infection can be made in this animal 5 to 14 days earlier than in the chick embryo. One strain of virus caused illness in mice 3 days after inoculation at which time elementary bodies were found without difficulty in smears of their brains.

F O MacCallum

Isolation of Virus of Lymphogranuloma Venereum from Blood and Spinal Fluid of a Human Being  
BEESON, P B, WALL, M J., and HEYMAN A (1946) *Proc Soc exp Biol., N.Y.*, 62, 306

The virus of lymphogranuloma venereum has been isolated frequently from inguinal buboes and from genital and rectal lesions, once from the spinal fluid of a patient with meningo-encephalitis and possibly twice from spinal fluid of two patients suffering from lymphogranuloma venereum. The virus has not previously been reported in the blood of man, though it has been found in the blood of experimental animals. The authors have now isolated the virus from the blood and spinal fluid of 1 of 8 cases of the disease, proved by isolation of the virus from buboes. The 8 patients were young coloured adults, 7 males and 1 female. Virus was isolated from buboes of 4 within the first four days—1 on the sixth day, 1 on the fourteenth day, and 2 on about the twentieth day of the disease. None showed evidence of meningeal involvement, and spinal fluid in all 8 cases gave normal cell counts and protein levels. The virus was isolated from the blood and spinal fluid of the 1 female on the sixth day of disease by inoculation on to the yolk-sac of chick embryos. This patient did not differ clinically from the others. Attempts to isolate virus from the blood and cerebrospinal fluid of the other proven cases were unsuccessful.

F O MacCallum

A Bacteriologic Study of the Resistance of Organisms Isolated from Cases of Non-specific Urethritis to Three Chemotherapeutic Agents  
WECKSTEIN, A M and RASMUSSEN, S H (1946) *Mil Surg.*, 99, 312

The authors set out to determine the nature of the organisms present in non gonococcal urethral discharges and to ascertain to what extent these

organisms are resistant to the usual chemotherapeutic agents. They found that a hemolytic *Staphylococcus albus* is present in over 68% of the cases, other organisms being present in lesser proportions. Sixty-five per cent. of all the strains were resistant to penicillin, 69.5% to neoarsphenamine and 95% to as much as 125 mg per 100 ml of sulphadiazine. Though there was no controlled follow-up the doctors treating the patients believed that their results agreed with the authors' *in vitro* findings.

[It would be interesting to know to what extent the organisms isolated in these cases are to be found in the urinary meatus of apparently healthy individuals.]

G L M McElligott

Abacterial Pyuria with Special Reference to Infection by Spirochaetes  
COUTTS W E and VARGAS-ZALAZAR, R (1946) *Brit med J.*, 2, 982

The problem of sterile, amicrobic, or abacterial pyuria has been of special interest to these authors who consider that the correct designation for this syndrome should be abacterial, and that the syndrome may originate from an ascending or descending infection of the urinary tract by viruses, spirochaetes, or protozoa. Failure to diagnose it has been due to the fact that the centrifuged urinary deposit has not been examined by dark-ground illumination.

According to the present authors' observations the bladder and kidneys may become infected by the ascending or descending routes. Spirochaetal (non syphilitic) infection of the male and female urethra is not uncommon. The descending infection is usually of the blood-stream type. Spirochaetes have been found in bladder urine in so-called war nephritis, trench fever, relapsing fever, and Weil's disease. The authors consider that the spirochaetes present in their cases were derived from the buccal cavity or the intestine. In all their cases the spirilla were of diverse morphology, some being slender with only a few spirals, while others were very similar to *Spirillum*. To demonstrate the presence of these fragile micro-organisms, slow and prolonged centrifugation of fresh bladder urine is recommended and the examination of the deposit under dark-ground illumination after the addition of a drop of normal saline at 37° C. which increases the movements of the organisms.

J Semple

Studies on the Biologic Relationship between the Causative Agents of Syphilis, Yaws, and Venereal Spirochetosis of Rabbits. II. Comparison of the Experimental Disease Produced in Rabbits  
MCLEOD C and TURNER, T B (1946) *Amer J Syph.*, 30, 455

This paper compares and contrasts the course of the disease in rabbits produced by inoculation with *T pallidum*, *T pertenue*, and *T cuniculi*.

It is evident that the 3 types of treponemal organisms are biologically closely related although they are not the same. The reactions produced in the rabbit by the 3 species of organisms have many

features in common the lesions develop in the same broad sequence and bear a superficial resemblance, and the serological changes are much the same. Although the lesions observed in each disease possessed certain similarities they were distinctive enough to permit differentiation of one infection from the other  
V E Lloyd

**Studies on the Biologic Relationship between the Causative Agents of Syphilis, Yaws, and Venereal Spirochetosis of Rabbits. I. Observations on *Treponema cuniculi* Infection in Rabbits**  
McLEOD, C., and TURNER, T. B. (1946) *Amer J Syph*, 30, 442

The authors report the results of a study, over a 3-year period, of the course of spontaneous spirochaetosis occurring after experimental inoculation of 200 rabbits with *T. cuniculi*. The clinical picture produced by *T. cuniculi* infection was similar in its general features to that of experimental infection with *T. pallidum* in the rabbit. Individual lesions varied strikingly, and although a few resembled those of syphilis and yaws most of them were typical of *T. cuniculi* infection alone.

Lymph-node transfers from rabbits infected by inoculation, both during active infection and after several months' latency, resulted in infection of the recipient rabbit in most instances. In general, the local and systemic lesions, the positive serological reactions a month after infection, and the high degree of immunity to reinoculation with the same species of organism produced a pattern resembling that of experimental infection with *T. pallidum*  
V E Lloyd

## PUBLIC HEALTH

**Some American Ideas on Venereal Disease Control**  
WILLCOX, R. R. (1946) *Brit med J*, 2, 825

The campaign against venereal diseases is being pushed less vigorously in Great Britain than in America, mainly because the British rely almost entirely on voluntary methods. In New York a certificate of freedom from venereal disease is essential before marriage, pregnant women have their bloods tested for syphilis, venereal disease is notifiable, treatment is compulsory, and women arrested for prostitution are subject to examination and treatment. Most cities have a control section, and every effort is made to trace contacts. In Chicago bar-keepers are invited to co-operate and if they do not are liable to be put out of business.

Prophylaxis is not pressed on the civilian, but Service men are well provided for. Some 4,000 reports of contacts or cases are dealt with monthly in Chicago, and, if letters fail, field workers are called in. The tracing of cases for follow-up is done by social workers at the clinics, and 70% of the first 3,000 cases of early syphilis are still under observation.

Propaganda is forceful. Trams and buses carry slogans, and book matches are used for the same purpose. A new type of advertisement is the "juke box," which alternates entertainment reels with control messages, and is provided free. A quarterly periodical entitled *V D Topics* is published, and the radio is used for talks. The list of activities would not be complete without mention of the American Social Hygiene Council.

[In spite of these activities it seems probable that venereal disease is more prevalent amongst Americans than among Britons, it is possible that Americans are more promiscuous than Britons, at any rate so far as Service men are concerned]  
T E Osmond

**Incidence of Yaws and of Venereal Diseases in Lango (Uganda)**  
HACKETT, C. J. (1947) *Brit med J*, 1, 88

A statistical analysis is made of data compiled from medical reports, out-patient attendance figures, and a serological survey of a gaol population and a station labour force. Two small towns in Uganda—Lira (a yaws area) and Masaka (a syphilis area)—are chosen for comparison, and further facts are forthcoming from the neighbouring town of Kampala itself. A survey of the district in 1931 showed that, of 24,000 children under 15 years of age examined, 3.9% were suffering from active secondary yaws—a condition readily observed in the children of nearly every Lango community. At Masaka congenital syphilis is frequently also seen. A comparison of the out-patient attendances in the two places over a 9-year period shows that at Lira the percentages of the average total yearly attendance were: due to yaws 20.9, to syphilis 1.1, and to gonorrhoea 0.6. At Masaka the percentages were: for yaws 1.6, syphilis 17.5, and gonorrhoea 2.5.

From various surveys it is concluded that in Lango the incidence of venereal disease is low, but that of yaws is very high, and few adults die without having contracted the latter disease.

R R Willcox

# THE EPIDEMIOLOGICAL CONTROL OF VENEREAL DISEASE\*

BY

SIR WELDON DALRYMPLE-CHAMPNEYS

*Deputy Chief Medical Officer, Ministry of Health*

In 1943 I was given the interesting but difficult task of conducting the Joint Committee on Venereal Disease, on which were represented the Admiralty, War Office, Air Ministry, Ministry of Health, the Department of Health for Scotland, the Home Office, the Metropolitan Police, and the Canadian and United States Armies. I will refer later to the work of this Committee, which was confronted with an extremely difficult situation having international implications. Though it met in an atmosphere charged with emotion, by reason of highly coloured press reports appearing both in this country and across the Atlantic about social conditions in London, the proceedings of the Committee were invariably marked by the most helpful and friendly spirit on all sides.

There can be few subjects larger and more involved than venereal disease, and in which it is easier to make mistakes of real importance. Nor does its narrowing down to the aspect of epidemiological control do much to simplify it, as it is impossible to discuss its epidemiology without considering many problems of a highly technical nature. I would, therefore, like to limit my remarks to observations and suggestions which may stimulate discussion and perhaps indicate the way in which a medical administrator with certain responsibilities in regard to the control of these diseases views the problems and difficulties of the specialist in venereal diseases.

I always try to regard the venereal diseases as merely a group, though admittedly a very special one, of the communicable diseases against which the health services of the country are constantly fighting. This attitude is not rendered any easier by the moral

questions involved, the conspiracy of silence which has hampered our work in the past but is now happily in course of suffering defeat, and the social implications of infection which can indeed be lessened by wise education but are an inseparable concomitant of diseases spread by sexual intercourse.

## Statistical Trends

In studying this group of communicable diseases—as with all infectious diseases indeed—one of the first things we need to know is its extent and distribution, by sex, age, and locality, and at once we encounter peculiar difficulties. Not only are the venereal diseases not notifiable in this country, but the ordinary methods for securing notification seem to carry with them a strong possibility, at least, of defeating their own object. It is often argued against this view that compulsory notification has been successfully employed in several foreign countries, notably in Sweden and in parts of the United States of America, but this success seems to me open to doubt in certain cases, and it depends inevitably on the public attitude, which varies with national characteristics and customs.

As you all know the efforts of venereologists and workers in public health were strikingly successful between the two wars, the number of cases of early syphilis dealt with at the treatment centres, for instance, having been reduced to 4,986 in 1939, a low record and over 45 per cent less than in 1931. Then, when hopes of further reductions were running high, came the late war with the rise inevitable in such circumstances, beginning slightly in 1940, but rising to a maximum in 1945 (5,527 for females as against 1,421 in 1939—an increase of nearly 389 per cent). I have

\*An address to the Medical Society for the Study of Venereal Diseases, April 26, 1947.

quoted the figures for females because of the well known difficulties in the case of males due to recruitment to the armed forces, but there seems little doubt that the trend is the same as for females. The figure I have given for females in 1945 represented a rise of 1,143 over that for 1944, and though the full figures for 1946 are not yet available it is clear that the increase in syphilis in 1946 was proportionately greater than that of any of the years immediately following the 1914-18 war, but such a rise occurred, we must remember, as long after the First World War as 1920, and should not I think occasion too much pessimism. After all we still have considerable numbers of infected men coming back home, not only for demobilization but also on leave from the B A O R, where conditions have not been too good.

The variations in the incidence of gonorrhœa are even more difficult to trace, owing to the greater frequency with which cases of this disease are treated privately. In the opinion of our expert advisers at the Ministry there was probably an increase in the incidence of gonorrhœa in males up to 1941, followed by a progressive decline, whereas in females the rise in incidence continued until 1944.

We are therefore confronted by the same sort of situation as after the 1914-18 war, but this is only superficially true as the circumstances are in reality greatly changed in three important respects. We now have new and powerful remedies which we did not possess in 1919, we already have improved facilities for treatment, and there is good reason to hope that the new National Health Service will enable us to use our facilities to much greater advantage than in the past.

#### New Remedies

First, then, let us consider briefly the new remedies. The sulphonamides undoubtedly caused a revolution in the treatment of gonorrhœa, but as with all revolutions there have been accompanying dangers and drawbacks. The rapid disappearance of symptoms in cases treated at the centres led to discontinuance of attendance in many cases before a cure was effected, and undertreatment has led to the emergence of sulphonamide-resistant strains. Though the alarm occasioned by the early reports from Italy has been partly allayed by our later experience at home,

yet the reality of the danger of sulphonamide-resistance will not, I think, be denied. On the other hand the markedly reduced incidence of impaired vision and blindness following the introduction of the sulphonamides in the treatment of ophthalmia neonatorum must be regarded as a solid gain for which we may be thankful.

Even more thankful should we be for the discovery of our second new and more powerful ally, penicillin, which has revolutionized the treatment not only of gonorrhœa but also of syphilis, even admitting that the time has not yet come when we can safely abandon the use of other older remedies in the treatment of this latter disease. But, to take gonorrhœa first, we seem at last to have a remedy in penicillin which when used properly can avoid to a very great extent the two drawbacks to the use of the sulphonamides—discontinuance of treatment and the creation of resistant strains—as a very large proportion of cases can be cured in a single day. We must, however, still be on our guard here, as penicillin tablets are being prescribed for the treatment of this disease, with the consequent possibility of thus creating penicillin-resistant strains, a danger on which it would be interesting to know the views of venereologists. Are we then in sight of a reduction of gonorrhœa to a position of relative unimportance, or will the spread of resistant strains dash all our hopes? Even if we succeed in killing the gonococcus easily and quickly in most cases, women may still be left with secondary infection, which to the patients themselves is the disease, whatever the change in bacterial flora we may have effected. Being at the Ministry the medical officer responsible for all matters concerning the antibiotics—or, as we prefer to call them, the anti-infective substances—I am firmly convinced that we are entering a new and unknown world and that the ultimate effect of eliminating, say, penicillin-sensitive organisms when non-penicillin-sensitive organisms are also present is still unknown, both as regards the individual and the community. Also, is the efficacy of penicillin in gonorrhœa going to encourage patients to risk infection subsequently? Who can tell? In the case of syphilis our difficulties are undoubtedly greater, and I should not be surprised to find that many specialists are unable to share the early optimism of the

American authorities in this matter. Whether we shall eventually be able, with improved methods of administration, to replace the older remedies entirely by penicillin I am not rash enough to guess, but for the present a more cautious view is taken by the Ministry of Health. Nevertheless a reduction of the treatment period from about a year to ten weeks thanks to penicillin is an enormous gain, and equally important, to my mind, is the possibility of being able to treat cases in out-patient departments by the use of either depot injections of oil-wax or ethyloleate suspensions, or two massive doses daily of penicillin solutions.

### General Measures for Control

I would turn now to general measures for bringing the disease under control, picking out for consideration a few individual aspects about which there is still a great difference of opinion.

**Public Education**—Let me take first the subject of public education, in the methods of which very important changes took place during the war years. In 1942 we eventually persuaded the B B C and the Press to make an experiment in frankness, though they had considerable misgivings which proved quite groundless, for public opinion had advanced much further than they suspected between the wars. The salutary effect of such propaganda is very difficult to evaluate, but I for one cannot doubt its reality. One evidence of such an effect is the increasing number of non-veneral cases attending treatment centres, from 39,008 in 1939 to 72,689 in 1944. This may be explained as being due either to the increased awareness of the public in general, in which case it can be deduced that a larger proportion of patients suffering with venereal disease attended the centres than would otherwise have been the case, or to an increased nervousness of the apprehensive and suggestive individuals in the population, with consequently no significant effect on those really suffering from these diseases. I think it is extremely difficult to determine which explanation is the correct one, and I cannot help feeling that it is right in the meanwhile to continue propaganda on the present lines whilst keeping a close watch to exclude features which would attract especially those persons for which the service is not primarily designed.

I am aware, of course, that a considerable burden is being placed on already overworked venereologists by this increased inflow of persons to the centres, especially as a large proportion of such persons—I have been told that it may amount even to 50 per cent—require treatment for some non-veneral condition. At the same time it is obviously within the objectives of the new National Health Service to secure treatment for such patients, and the remedy seems to be to refer them to other appropriate departments rather than to discourage their attendance.

**Contact-tracing and Follow-up**—Perhaps no aspect of control is more important than contact-tracing and follow-up, and in this connexion I would say a word about that highly controversial measure Regulation 33B. I am not ashamed to own that I played a large part in its production and that I still believe that it was worth while. In fact even if it had had no other effect than to secure the treatment of a limited number of anti-social or mentally defective sources of infection it would in my opinion have been justified, especially in war-time, but its stimulating effect on contact tracing has, perhaps, been equally valuable. This latter result was, of course, greatly enlarged by the encouragement given by the Ministry to Medical Officers of Health to take action on the receipt of a first notification. In 1945 of the 8,757 persons reported as contacts once under this Regulation 3,893 were traced, of these, 3,117 were persuaded to submit to examination. Considering the limited field covered by this procedure and the staff difficulties of medical officers of health this is far from being a negligible contribution to the ascertainment and eradication of the disease. The figures for those cases on which two or more reports were received are, of course, far smaller, viz. 1,030, of whom 294 were persuaded to undergo examination and 483 were served with Form 2, resulting in 401 of these latter persons being examined. In connexion with this work many social workers have been appointed by Local Authorities not only to trace those reported under the Regulation and persuade them to submit to examination and if necessary treatment but also to persuade voluntary patients to get their contacts to come for examination, to follow up defaulters and to help patients to

overcome all the innumerable social difficulties in the way of regular attendance at the centres. This service, though of course in existence before the Regulation was devised, has certainly derived a valuable stimulus from its passage.

None will deny, I think, that so far as local contacts go the patient himself is the best tracer, but the contacts are not always local, and anyhow the patient needs encouraging and the contact has to be followed up in many cases, so these social workers are vitally necessary. Should they be health visitors, venereal disease almoners, or who? The general opinion, I believe, and certainly my own, is that the ordinary women officers of the Local Authority, that is, health visitors, school nurses, tuberculosis visitors, or persons combining several of these functions, are the most suitable persons to trace the contacts in the first instance, as their visit to a house excites no particular remark and it is easy for them to make some banal enquiries and wait their opportunity to introduce the subject of venereal disease. But the special training and experience of the venereal disease almoner makes her ideal in most instances for following up defaulters—a somewhat inappropriate word perhaps for persons who often fail to continue attendance through no fault of their own.

#### Joint Committee on Venereal Disease

There are finally three subjects on which my Joint Committee on Venereal Disease made recommendations.

**Blood-testing**—First they recommended that efforts be made to secure the adoption of the principle of routine blood-testing for syphilis in the case of every pregnant woman, and that the laboratory services should be extended accordingly and welfare authorities be urged to use them. This recommendation was made not with the idea of considering every woman who gave a positive blood test as being syphilitic, but rather as requiring full examination to establish a diagnosis. This seems to me a very reasonable attitude, and I hope that in time such an examination will become a routine throughout the country. I am, of course, keenly alive to the necessity of a

high standard of laboratory work in this connexion.

**Congenital Syphilis**—Secondly, they recommended the compulsion of parents and guardians of congenital syphilitic infants and children to secure for such children continued treatment until the risk of late effects is eliminated. Further they recommended compulsion of parents of syphilitic infants and children, and of infants suffering from gonococcal ophthalmia, to themselves undergo examination and any necessary treatment to prevent further transmission of these diseases to these or other children. Such a measure was regarded by the Committee as being a form of compulsion for which quite special justification could be alleged and one which would, they believed, meet with widespread public support. In this sense it was independent of other kinds of compulsion which the Committee were not prepared to recommend at the time, but which they did not wish to exclude permanently. The Minister's Medical Advisory Committee, on the recommendation of a Venereal Disease Sub-Committee, accepted the principle of my Committee's recommendation on this point, but thought it "doubtful whether the elaborate legal and administrative arrangements necessary would be justified by the results obtainable." Consequently no action was taken on our recommendation.

**Prostitution**—Lastly (they made many other recommendations which cannot be dealt with here) they recommended that the Ministry of Health be urged to institute immediately a thorough investigation into the whole subject of prostitution with a view to putting the public in possession of the facts, and thereby educating public opinion and securing its support of measures designed to reduce the danger of the spread of venereal disease by prostitution in all its forms. This seemed to me a most important recommendation and I had hoped, with the aid of one or two others, to carry out such an investigation myself. Unfortunately pressure of work made this impossible, though I still hope it may take place. I am a firm believer in the efficacy of giving the public the plain unvarnished facts when any action is required that cannot succeed without their active support. It may perhaps be objected that the facts with regard to prostitution in

this country are well known to all those interested, or secondly, that no practical action could be taken which is not already being taken, even if a public demand should be created.

With regard to the first of these objections it may be interesting to note that, although all the members of the Joint Committee on Venereal Disease were experienced and knowledgeable workers in this field, many of the facts presented to us by the representatives of the Metropolitan Police and the Home Office were new to us. As regards the second objection, whilst we found the legal and administrative problems presented by prostitution even more complicated than we had

supposed, yet we felt that certain measures which would not in the present state of public ignorance be tolerated by Parliament or the electorate would be likely to win support if all the facts were known, and that an important advance would be possible not only, or perhaps chiefly, by means of legal enactments, but by public support for the implementation of existing powers and public condemnation of practices now tolerated through ignorance or indifference.

I wish I could say more on this important and difficult subject, but I wish even more that I were in a position to give the full facts, free from emotion or prejudice, scientifically—but mercilessly.

## DISCUSSION ON THE PRECEDING PAPER

DR G. L. M. McELLIGOTT (the President) said that Sir Weldon had given them a most interesting address. The most impressive result of sulphonamide treatment was the great decrease in the number of complicated cases of gonorrhœa. A careful survey, carried out at St. Mary's Hospital at the end of the first year of sulphonamide therapy, had shown that the incidence of complications of gonorrhœa, in both men and women, was only about one eighth of what it had formerly been.

With regard to oral penicillin tablets, he saw that such tablets were now on the market. One great danger was that they might not be taken as directed, and that if they became as easy to obtain as the sulphonamides had become there was a danger that syphilis might be masked.

He did not agree with the suggestion that non-venereal cases should invariably be referred to other departments of the hospital, which often did not have the facilities for dealing with these conditions. In most hospitals the best place for treating trichomonas infestation was undoubtedly the venereal diseases department. Another point was that the tests for the exclusion of gonorrhœa in women would often take as long as the curing of the original complaint.

MR A. J. KING said that he was particularly glad that Sir Weldon had stressed the importance of telling the public the whole truth and nothing but the truth.

Inevitably there must be a divergence of viewpoint between the public health expert and the clinician. The public health expert was apt to take the attitude that one only had to find the patients—to shepherd the sheep into the fold, so to speak—and 100 per cent. cure was certain and the problem was solved. A great deal of money had been spent on propaganda which would have been better spent in promoting the study of the fundamental pathology of these diseases of which

a great deal was still unknown. Even careful and conscientious treatment left a proportion of cases with latent infectious disease. This applied particularly to the group of diseases which are called primary non-specific infections. These were communicable and gave rise to serious complications. They were moreover recurring diseases which, on the whole, were not very susceptible to treatment.

Which diseases were to be included among the venereal diseases? The problem was a very much greater one than the official pronouncements on the subject suggested, and the proposal that those patients who were not suffering from syphilis, gonorrhœa, or chancroid, should be turned over to other departments of a hospital was not a practical one. The other departments of the hospital would wish to have nothing to do with them and if such a course were attempted it would result in extraordinary confusion, and the patients would be the sufferers. With regard to the methods of compulsion which were being advocated, was it not a fact that for the most part the only patients who refused examination and treatment when told that they were probably infected were the dull and backward, the mentally defective, and the psychopathic? When these patients were brought for treatment it often happened that they stayed for a day or two and then disappeared. Nothing could be done about such patients unless they could be detained in proper institutions. Just to get them into hospital was quite ineffective; they had to be kept in and there was no provision for that in 33B.

Most would probably agree that the parents of infected children should be compelled, at the least, to see that their children were brought regularly for treatment. Again, those parents who were difficult in this matter were usually of the defective type, and it was not easy to deal with them. There was a case for having some regulation whereby such



children could be taken away from their parents and put in appropriate institutions if necessity arose

DR FORGAN said Sir Weldon had mentioned that his Committee's discussions had taken place in a rather emotional atmosphere, but, in spite of that, the members had co-operated well. Their own Society had been founded in a highly emotional atmosphere and such a discussion as they were having that afternoon would have been, in those early days, *ultra vires*. The fact that they were discussing this subject today was a sign that some progress had been made during the last twenty-five years.

Sir Weldon doubtless knew that he was speaking to the converted, for the Society had unanimously passed a resolution in favour of measures of further control. It was to be hoped that Sir Weldon was right in his view that the introduction of the new National Health Service was going to make easier the control of venereal diseases. His Committee in its recommendations did not exclude for ever the possibility of arming local authorities with powers to be used in the rare cases where the exercise of such powers would be in the public interest. Progress towards the control of these diseases was very slow. They ought to ask themselves as individual citizens of what there was to be afraid. Politicians were more afraid than anyone else. He did not think it mattered what political complexion the Government bore, no Government was prepared to grasp this nettle.

COL L. W. HARRISON said he agreed with the two measures of compulsion recommended by Sir Weldon's Committee viz. that parents of infected children should be treated, and that parents and guardians of children with congenital syphilis should be compelled to take their charges for treatment. But the older he grew the more opposed he was to any general measure of compulsion. We had been bidden *ad nauseam* to follow the example of compulsionist countries such as Sweden and Denmark, but how had these fared during the war? In his view, no better than Great Britain. He quoted figures which showed that in Sweden the number of new cases of syphilis had been more than twice as many in 1944 as in any of the immediately pre-war years. In Denmark in 1940 there had been 498 new cases of syphilis, but in 1944 the number was 2,225, thus compulsory laws reinforced by the iron discipline of the Nazis had not prevailed against war conditions.

The routine testing of pregnant women had been practised a great deal in this country long before the late war.

Concerning incidence in this country, he himself had been interested to note that the increase in England and Wales seemed to have occurred more in the ports than in the inland towns. Comparing seven ports and seven inland towns, each group having approximately the same population of about three million, the number of male cases of early syphilis in the period 1939 to 1944 was 7,901 in the ports and 2,835 in the inland towns. Of

female cases of early syphilis in the same period, there had been about twice as many (4,100) in the ports as in the inland towns (2,064), there had not been a corresponding increase in congenital syphilis in children under one year of age.

He thought that penicillin tablets were a public danger owing to the risk of under-dosage which their indiscriminate use by the general public without medical guidance would entail.

With regard to Regulation 33B, this was introduced for the protection of the Armed Forces, and he did not think it would be much used in civilian work.

He thought that more attention should be concentrated on persuading the original patient to bring his or her contact for treatment, it was a far cheaper method of contact-tracing than visiting by social workers.

DR McLACHLAN suggested that, while a large number of clinics in this country had reasonable schemes of treatment, this was by no means universal. Itinerant patients often got different instructions at different clinics. This was particularly noticeable among seafarers treated partly in this country and partly in foreign ports.

The Society might usefully sponsor various schemes of treatment which would be regarded as "standard". The efficacy of the present schemes of treatment could only be assessed on the end-results of a sufficient number of cases, and this could best be done by some central body such as their Society.

DR DOUGLAS CAMPBELL referred to standard courses of treatment as given in the Army. Although these were sometimes resented by other venereologists requested to continue the treatment, in many cases the results were good. It might be worth while, speaking internationally, if an agreement could be reached whereby a patient who had started treatment in one place could be assured of the continuation of the same treatment when he moved elsewhere. He thought that the clinician who first saw the patient should have a certain right of suggesting the treatment to be followed by other clinicians. The question of control, especially in the case of children, should be pressed. At the moment there was a very good health service for school-children, but there was no power to bring a child up for treatment, and often they had to rely on the help of purely voluntary bodies, such as the National Society for the Prevention of Cruelty to Children, in order to get these children to the clinics for the necessary treatment.

On the controversial matter of prostitution, his experience had been mainly in provincial towns where no great number of infections were forthcoming from the frank prostitute. Abroad, of course, the prostitute was a very great danger. Only in one town did he see the control of prostitution do good, and that was Algiers, a town in which there was no casual promiscuity. The troops could be exposed only in brothels, and the brothels in that town were relatively well looked after.

DR MACFARLANE thought that government propaganda had little or no influence on infected individuals who belong to that section of the community which constitutes the most fruitful source of venereal infection in the country. The value of paper propaganda would appear to be restricted in the main to those who run the risk of acquiring disease but who eventually are classified as non venereal.

While he could not support compulsory treatment for all types of venereal diseases, the pregnant woman suffering from syphilis should be compelled to attend for treatment, assuming that no valid excuse could be given by the individual and that reasonable social efforts had been made to persuade the patient to co-operate.

SQUADRON LEADER HOBBS said that he was in Germany recently and he found that since treatment by penicillin had been available there was a relative increase of syphilis in proportion to gonorrhœa.

THE PRESIDENT remarked that from a preliminary scrutiny of the figures for 1946 the syphilis ratio did appear to be getting smaller.

DR. CURTIS said that it was the experience in Germany and Denmark that the increase of syphilis in the war years was in proportion far greater than the increase in gonorrhœa. In Germany during 1946 the ratio of syphilis to gonorrhœa was about 1 to 3 or 2.5 in the civilian population. He agreed with what Sir Weldon had said, that the health visitor was to be preferred to the *ad hoc* venereal diseases visitor. He would go further and say that this applied also to the tracing of defaulters. The venereal disease almoner soon became known in the areas where she worked and such was the urge to conceal the fact of venereal disease that there was a danger that the work of the *ad hoc* social service worker might result in less good than that of the all purpose health visitor.

DR W N MASCALL said that he had always been a strong advocate for the routine Wassermann test in all pregnant women, and he believed that it should form part of the routine ante natal supervision. He remembered when the London County Council decided to discontinue their routine testing. This action was partly due to the result of a survey on congenital syphilis, in which it was shown that the number of positive Wassermann reactions found in women attending ante-natal clinics was small and partly due to the fact that the necessary laboratory facilities were not available. Before large scale examinations could be carried out more specially trained pathologists would be required, and possibly some standardization of the tests would be advisable if reliable results were to be obtained. The difficulties might be overcome by the setting up of central laboratories in some areas.

The results of blood tests as seen on the transfer books of patients from all over the country were most confusing. Half the notations could not be

understood and the results tabulated perhaps at weekly intervals varied so considerably that no reliable deductions could be made from them.

He wondered whether sufficient time had yet elapsed to draw any definite conclusions about the end results of treatment with penicillin. There was an incredible disparity in the dosage employed in various clinics which added considerably to the difficulty in assessing the real value of this therapeutic reagent.

DR HEYWOOD said that on the question of standardized treatment the Ministry had already made one recommendation on those lines. What was really needed was a standardization of follow-up after penicillin therapy. Col Harrison's comparison of venereal disease figures of Scandinavian countries with those of this country was not a valid argument against compulsory measures. In the case of Sweden where the increase was not so great as in this country it had been necessary during the war to maintain a large standing army and navy which, though subject to military discipline came outside the scope of the compulsory civilian measures. So far as Denmark was concerned, the manifold increase in syphilis which up to the outbreak of war had become a rarity could hardly be attributed to a failure of compulsory methods since the whole of the Danish Police Force had been in German concentration camps from 1942 onwards.

He thought that Regulation 33B had become essential and that it needed strengthening, especially in compelling syphilitic children to attend for treatment, and also with regard to expectant syphilitic mothers. But before they applied for further compulsory powers he thought they must set their house in order and obtain a uniform standard of diagnosis and treatment. They must have a better laboratory service than they had at present.

DR. R. M. WARREN said that he had been asked to address various sections of the community on this subject, the audiences being Service men, Red Cross and St John workers, Factory workers, and boys clubs. They had received very eagerly any information he could give them. He suggested that propaganda must be continuous and not in the form of spasmodic campaigns.

An essential prerequisite of any measures to improve case finding and holding was an improvement in the facilities for diagnosis and treatment. Surely, now that the National Health Service was on the threshold, the opportunity might be taken to bring the venereal disease service throughout the country up to the level of the best now obtaining. Certain minimal standards should be laid down as to equipment and staff, treatment, and follow up.

DR ATLAS said that he himself had been educated on the Continent, and when he came to Great Britain he was amazed at the attitude towards venereal disease and to venerology as a speciality which was treated like a Cinderella in the realm of medicine. Compulsory treatment of venereal

diseases certainly gave good results. The statistical figures given by Col Harrison for the Scandinavian countries, particularly the small numbers of syphilis cases before the war, proved the point. In the British Army the treatment of venereal diseases was very well organized, and there always was a certain degree of compulsion towards treatment. The results of treatment in the Army had been very good and the percentage of people who could slip through without any treatment had been small. In this country at present most of the treatment was done in out-patient departments and there was great difficulty in getting patients admitted to hospitals. If patients could only be treated in hospital, and if every venereal disease clinic could have wards with beds attached, it would be a great advantage. It was a matter for the health authorities to provide beds

DR D I WILLIAMS, on the question of penicillin for treating venereal disease, said that one could up to a point draw a parallel with sulphonamide tablets. Patients would always prefer tablets to injections, and he supposed that penicillin tablets would not always be given at three-hourly intervals. One of the dangers was that patients might use the drug privately and get resistant strains of the organism and perhaps disguise their syphilis.

He suggested a proper research unit in venereal disease.

SIR WELDON DALRYMPLE-CHAMPNEYS, in reply, thanked the members for the information they had given him that afternoon. A number of interesting points had been raised. One point on which he had been rather criticised was his suggestion that the venereal disease clinic was being somewhat overwhelmed by non-venereal cases and that sooner than discourage patients from coming it would be better to distribute them to other departments of the hospitals. By this he did not mean that in the present circumstances it would be a good thing that these patients should be sent automatically to the other departments. What he meant was that, as the service developed and as the co-ordination of the Health Service proceeded, there might be a certain number of cases which in time could be referred to other departments. These departments by then would have been staffed and equipped for dealing with such cases. But apparently the members of the Society appeared to be anxious to stick to these cases, and he hoped they would, because he was sure they would deal with them much more efficiently than anybody else.

He had thought that venereal diseases were diseases which were or might be contracted in the act of sexual intercourse. One of the things he had learnt that afternoon was the importance of further research into what might be called "minor" venereal diseases. It was their job in his service to try to provide the necessary mechanism which would bring them into the field, along with the facilities to enable experts to deal with them when they got there. The part of medical administration was not to treat the patients but to help other people to obtain the facilities for such treatment.

He quite agreed with all that had been said

about the difficulty of keeping patients under treatment, and obviously unless there was some degree of compulsion this could not be done. These mentally defective and anti-social patients were a great difficulty. He was not against compulsion, but doubted only whether at the present moment compulsion would work or give them more than they would lose. The whole question of the effectiveness and the need of compulsion depended very much on the state of public education and the public attitude. Such attitude changed very rapidly. The history of venereal disease publicity showed the extraordinary pace at which the public outlook had changed.

A very important point was about the need of getting some uniformity in treatment. There was also need for uniformity in nomenclature. He understood and sympathized with those who dreaded too much standardization. This was a thing to guard against, particularly at the present time. He thought there was considerable danger that if they were not careful they would all get into one stamp and one mould. Nevertheless, there was a modicum of standardization without which nothing could be achieved at all. They ought all to agree, whatever their particular speciality was, to arrive at some sort of uniformity at any rate in the recording of the cases.

Some speakers appeared to think that he was claiming more for Regulation 33B than he was. It was a war-time measure and was necessary from that point of view, but he never imagined for a moment that it would cover the whole field or present a permanent solution of the problem.

With regard to the dangers of prostitution, he agreed that in the provinces the problem was not the same as in London, where conditions were very different. But while he agreed that prostitution was a very important channel for conveyance of venereal disease, and one which ought not to be tolerated in any self-respecting city to the extent and under the conditions in which it was tolerated, he felt that measures of control were extremely difficult.

He was interested in what had been said about the venereal disease almoners becoming well known, and, of course, the smaller the neighbourhood, the better known they became. He believed that the co-ordination of work under the new National Service might become a very valuable means of making the venereal disease services more easily available, better housed, better equipped, and better served in every way. The intention was that all services should be co-ordinated for the public good. From the venereal disease clinic point of view he would have thought that any plans for the future were likely to bring advantages. His experience was that the venereal disease department was often very badly housed in the hospital.

In speaking of routine Wassermann tests he did put in a proviso that there must be efficient laboratory services. If they were suddenly to introduce tomorrow Wassermann testing of all pregnant women there would not be the laboratory services available to carry it out, but there was every intention of providing such services to do this.

# THE HARRIS SLIDE TEST

## A MICROFLOCCULATION TEST FOR SYPHILIS WITH CARDIOLIPIN ANTIGEN

BY

THOMAS M VOGELSANG

— *From the Department of Bacteriology, Gade's Institute, Bergen, Norway\**

The antigens in common use for the serological diagnosis of syphilis, such as the complement fixation tests and the various flocculation tests, are alcoholic extracts of ox heart usually sensitized with cholesterol. If, however, cholesterol is added to the crude alcoholic extract, false positive reactions are not uncommon. On this account it has become customary to purify the alcoholic extracts of ox heart by first undertaking an extraction with ether, acetone, or ethylene perchloride to remove adventitious substances. But even these purified antigens, which contain the potent phosphatides, are not completely rid of non-specific substances.

Of late years the active lipoid antigen constituents have been subjected to searching studies. It was not, however, until 1941, when Mary C Pangborn succeeded in isolating a hitherto unrecognized serologically active phospholipid, cardiolipin, from ox heart, that an antigen consisting essentially of chemically pure substances was produced. Used alone as an antigen, cardiolipin is anti-complementary. Mixtures of cardiolipin and purified lecithin have, however, been found highly antigenic, and when cholesterol is added to such mixtures sensitization is attained.

Cardiolipin-lecithin-cholesterol antigens have been used in the complement fixation tests for syphilis by Harris and Portnoy (1944) and by Maltaner and Maltanef (1945), and also for various precipitation methods by Brown (1944, 1945), by Rein and Bossak (1946), and by Kline (1946). The cardiolipin-lecithin-cholesterol ratio has varied in the different techniques employed.

Harris and others (1946) have described a new microflocculation test for syphilis. They use cardiolipin antigen and their test possesses the merit of simplicity. Its findings can be read in a short time. It should, therefore, be suitable for small as well as for large well-equipped laboratories. It is said to be characterized by satisfactory sensitivity and specificity, and at the same time to possess the merit that all test solutions are standardized.

Harris and others have referred to the test as the V D R L slide test—an abbreviation of the name of the laboratory in which it was devised—the Venereal Disease Research Laboratory, U.S. Marine Hospital, Staten Island 4, New York. In conformity with current practice in connexion with other flocculation tests, I have ventured to call this the Harris Slide Test in token of its discoverer.

This new test has been carried out at Gade's Institute on 5,556 sera, side by side with the three tests employed as a matter of routine: that is, the Bordet-Wassermann, the Kahn standard test, and the Meimcke clarification test No. 2. A short account of the results obtained is given in this communication.

### Technique

Briefly, Harris has shown that maximum reactivity, associated with good negative results, was obtained with an antigen in which one part of cardiolipin was combined with nine parts of lecithin and thirty of cholesterol. Thanks to the courtesy of Dr. Harris, we have been supplied with this antigen from the Venereal Disease Research Laboratory. Its formula is as follows:

Cardiolipin	0.03 per cent
Lecithin (approximately)	0.27 per cent
Cholesterol	0.9 per cent
Absolute alcohol	q.s.

\* Chief Thomas M. Vogelsang, M.D.

The antigen is diluted by the addition of buffered saline solution containing 1 per cent sodium chloride

Formaldehyde, neutral, reagent grade	0.5 ml
Secondary sodium phosphate ( $\text{Na}_2\text{HPO}_4 + \text{H}_2\text{O}$ )	0.093 g
Primary potassium phosphate ( $\text{KH}_2\text{PO}_4$ )	0.170 g
Sodium chloride, A C S	10.0 g
Distilled water	1000.0 g
Final pH	6.0 $\pm$ 0.1

Antigen and buffered saline are dispensed in screw-cap bottles and stored in the refrigerator

**Preparation of Antigen Emulsion**—Antigen emulsion is prepared by pipetting 0.4 ml saline to the bottom of a 30 ml round bottle and adding 0.5 ml antigen, drop by drop, from a 1.0 ml pipette (graduated to the tip) while the bottle is being rotated on a flat surface. The last drop of the antigen is blown from the pipette, without touching the saline, and rotation is continued for 10 more seconds. Add 4.1 ml saline (from 5.0 ml pipette) place top on bottle, and shake vigorously for 10 seconds. Antigen emulsion is then ready for use and may be used for one day if stored at room or refrigerator temperature.

**Preparation of Slides**—Glass slides (2×3 in.) with 12 paraffin wax rings of approximately 15 mm inside diameters are used. Paraffin wax rings are made by transferring the heated wax to the slides with metal moulds.

**Qualitative Serum Test**—The test is performed as follows

1. Pipette 0.05 ml heated serum into one ring of a paraffin-ringed glass slide
2. Add one drop (approx. 1/60 ml) antigen emulsion into each serum with the help of a 1-ml syringe fitted with a long needle
3. Rotate slides for four minutes by hand on a flat surface. This movement should roughly circumscribe a two-inch circle 120 times per minute
4. Tests are read immediately after rotation

**Reading and Reporting Test Results**—Tests have been read with the help of a powerful lens. Harris recommends microscopic readings at a hundred times magnification. Antigen particles, in properly prepared emulsions, appear as short rods. Aggregation of these particles into large or small clumps is interpreted as degrees of positivity. Clumping of these particles should be reported as follows

Reading	Report
No clumping or slight roughness	Negative (—)
Small clumps	Weakly positive (±)
Medium and large clumps	Positive (+)

When a magnifying glass is used, there is, as a rule, a definite difference between negative and weakly positive sera. The reading is easy, and only in a few doubtful cases does it depend on the personal judgment of the investigator.

## Results

The 5,556 sera are classified in two groups according to the presence or absence of any mention of syphilis in the notes accompanying them. The first group, with evidence of syphilis, included 777 sera with a history and/or clinical signs of syphilis, both treated and untreated. The other group, with no evidence of syphilis, included the remaining 4,779 sera from persons about whom available data provided no evidence of syphilis. In 259 of these there were no data whatever.

## Comparisons with Other Tests

**Bordet-Wassermann Test (Table I)**—Of 777 sera from known cases of syphilis, 636 recorded results which agreed when tested by the Harris and Bordet-Wassermann reactions (81.85 per cent). Among the remaining 141 sera, there were 37 giving a positive reaction, 63 giving a weakly positive reaction, and 41 a negative reaction to Harris, whereas 76 gave a positive, 23 a doubtful, and 42 a negative reaction to Bordet-Wassermann. The latter, according to these observations, gave a considerably greater number of definitely

TABLE I  
COMPARISON OF THE HARRIS SLIDE TEST WITH THE BORDET-WASSERMANN REACTION

	Evidence of syphilis	No evidence of syphilis
Harris +, B-W R +	281	27
Harris ±, B-W R ±	10	1
Harris —, B-W R —	345	4,690
Total	636	4,718
Harris +, B-W R ±	13	1
Harris +, B-W R —	24	3
Harris ±, B-W R +	45	7
Harris ±, B-W R —	18	7
Harris —, B-W R +	31	30
Harris —, B-W R ±	10	13
Total	141	61
Grand Totals	777	4,779

positive results than did the Harris test. If we also include the weakly positive results among the positives, the two tests show approximately the same sensitivity.

Among the 4,779 sera without syphilis data, 4,718 recorded similar results when tested by the Harris and Bordet-Wassermann reactions (98.72 per cent.) Among the remaining 61 sera there were 4 giving a positive, 14 a weakly positive or doubtful, and 43 a negative reaction to the Harris test, whereas there were 37 giving a positive, 14 a doubtful, and 10 a negative reaction to the Bordet-Wassermann. According to these findings, the Harris test would seem to be somewhat more specific than the Bordet-Wassermann reaction.

**Kahn Standard Test (Table II)**—Among the sera from known cases of syphilis there were 641 reacting in the same way to the Harris and the Kahn tests (82.5 per cent.) Among the remaining 136 sera there were 57 giving a positive, 45 a weakly positive, and 34 a negative reaction to the Harris test, whereas there were 49 giving a positive, 52 a doubtful, and 35 a negative reaction to the Kahn test. The sensitivity of the two reactions would, therefore, seem to be approximately similar.

Among the 4,779 sera without syphilis data there were 4,731 reacting in the same way to the Harris and the Kahn tests (96.69 per cent.) Among the remaining 48 sera giving conflicting results, there were 9 giving a positive, 11 a

TABLE II  
COMPARISON OF THE HARRIS SLIDE TEST WITH THE  
KAHN STANDARD TEST

	Evidence of syphilis	No evidence of syphilis
Harris +, Kahn +	261	22
Harris ±, Kahn ±	28	4
Harris -, Kahn -	352	4,705
Total	641	4,731
Harris +, Kahn ±	36	5
Harris +, Kahn -	21	4
Harris ±, Kahn +	31	3
Harris ±, Kahn -	14	8
Harris -, Kahn +	18	11
Harris -, Kahn ±	16	17
Total	136	48
Grand Totals	777	4,779

TABLE III  
COMPARISON OF THE HARRIS SLIDE TEST WITH THE  
MEINICKE CLARIFICATION REACTION

	Evidence of syphilis	No evidence of syphilis
Harris +, Meinicke +	288	22
Harris ±, Meinicke ±	17	5
Harris -, Meinicke -	320	4,686
Total	625	4,713
Harris +, Meinicke ±	16	4
Harris +, Meinicke -	14	5
Harris ±, Meinicke +	47	4
Harris ±, Meinicke -	9	6
Harris -, Meinicke +	50	35
Harris -, Meinicke ±	16	12
Total	152	66
Grand totals	777	4,779

weakly positive, and 28 a negative reaction to Harris, whereas 14 gave a positive, 22 a doubtful, and 12 a negative reaction to the Kahn test. These observations suggest that here, too, the Harris is somewhat more specific than the Kahn test.

**Meinicke Clarification Test (Table III)**—Among the sera from known cases of syphilis there were 625 reacting in the same way to the Harris and the Meinicke reactions (80.44 per cent.) Among the remaining 136 sera there were 30 giving a positive, 56 a weakly positive, and 66 a negative reaction to the Harris test, whereas there were 97 giving a positive, 32 a weakly positive, and 23 a negative reaction to the Meinicke test. It will thus be seen that the Harris test gave much fewer definitely positive results with syphilitic sera than the Meinicke test, whose sensitivity seems, therefore, greater than that of the Harris test.

Among the sera without any data of syphilis there were 4,713 reacting in the same way to the Harris and the Meinicke reactions (96.11 per cent.) Among the remaining 66 sera there were 9 giving a positive, 10 a doubtful, and 47 a negative reaction to the Harris, whereas 39 gave a positive, 16 a doubtful, and 11 a negative reaction to the Meinicke. It would thus seem that the specificity, in contrast to the sensitivity, of Harris is considerably better than that of the Meinicke.

**The Three Other Tests in the Various Stages of Syphilis (Table IV)**—In the first five groups in this table we find the numbers of the sera from the different clinical stages of syphilis. This grouping of the material has made the numbers within each group rather small, but on the whole it may be claimed that there is a quite good conformity between the results of the tests. In those cases in which there have been conflicting results, it was nearly always one or more of the other tests which failed and not the Harris. Also in the case of primary syphilis, the Harris would seem to be as good as the three other tests. Among the eight cases of primary syphilis with conflicting results there was one in which the *Meinicke* failed, four in which the *Harris* did so, five in which the *Bordet-Wassermann* did so, and six in which the *Kahn* failed.

In a group by themselves I have included the various forms of syphilis undergoing specific treatment at the time of the examination and the sera received for examination either at the completion of a course of treatment or for the purpose of control during the four ensuing years. I have grouped as latent syphilis the cases which had received specific treatment more than four years earlier without having subsequently received treatment or having presented clinical signs of this disease.

Among 119 cases of latent syphilis examined, there were 22 reacting in different ways to the four tests. Nine of these sera gave positive reactions to three of these tests, and among them there was only 1 in which the *Harris* failed.

There were greater discrepancies between the different tests when we dealt with treated syphilis than when we did so with the clinical, untreated forms and with latent syphilis. Among 442 treated cases in the various stages of syphilis, there were 103 which reacted in different ways to the respective tests, but 39 of them were *Harris*-positive. Among the 26 sera giving positive reactions to three tests there were only four in which the *Harris* failed.

Thus altogether 777 sera from cases of treated and untreated syphilis were examined. In 627 of these sera (80·7 per cent) the reactions were identical in the four tests, being positive in 326, negative in 301. Conflicting results were obtained with 150 sera (19·3 per cent). Of the 46 sera giving positive reactions to three tests, 41 were positive to the *Harris* test. Altogether the *Harris* was positive in 65 of these 150 sera giving conflicting results.

Of the 777 sera from patients with syphilis data

391 were positive for the *Harris* (50·32 per cent),

390 were positive for the *Bordet-Wassermann* (50·19 per cent),

390 were positive for the *Kahn* (50·19 per cent),

434 were positive for the *Meinicke* (55·85 per cent).

**The Three Other Tests of Sera with no Evidence of Syphilis (Table V)**—Among the sera from persons with no syphilis data there were 1,544 sent for the control examination of

TABLE IV

COMPARISON OF THE HARRIS SLIDE TEST WITH THE THREE OTHER REACTIONS IN THE DIFFERENT STAGES OF SYPHILIS

Sera from cases of syphilis	No of sera	Identical results			Conflicting results			
		No of sera	+	—	No of sera	Number of positive reactions		
						3	2	1
Congenital	19	13	13	—	6	—	4 (4)	2
Primary	41	33	21	12	8	2 (2)	4 (1)	2 (1)
Secondary	47	46	46	—	1	1 (1)	—	—
Tertiary	76	69	69	—	7	5 (5)	2	—
Cerebral	33	30	29	1	3	3 (3)	—	—
Latent	119	97	29	68	22	9 (8)	6 (1)	7
Treated	442	339	119	220	103	26 (22)	43 (7)	34 (10)
Total	777	627	326	301	150	46 (41)	59 (13)	45 (11)

( )—Number of positive Harris Slide Tests

pregnant women in accordance with Norwegian law. Among these sera were 10 giving positive reactions to all the tests, and 15 giving conflicting results, with the reaction to the Harris positive in only 2 cases.

There were 530 sera from healthy persons needed as blood donors or requiring health certificates or the like. In 526 of these sera the reactions were negative to all the tests. Among the remaining four sera giving conflicting results, there was one positive to the Harris.

It is said that there is a tendency for false positive reactions to be associated with diseases of the lungs and acute infections, and the sera from such cases have, therefore, been grouped separately. Of the 11 sera from patients with such diseases and showing conflicting results, 4 were positive to the Harris.

Among 2,033 sera from patients suffering from various diseases without syphilis data there were 53 giving conflicting results with the four tests. Only 7 of these sera were positive to the Harris.

No data whatever were available in connexion with 259 sera, among which one might, therefore, expect to find cases of known syphilis treated or untreated. Twelve of these sera gave positive reactions to all 4 tests, and 3 were positive to 3 tests, which in two cases was the Harris test. Two were positive to the Bordet-Wassermann and to the Meinicke, but negative to the Harris and the Kahn. Six were positive to only one test which in 3 cases was the Bordet-Wassermann, in 1 the Meinicke, and in 2 the Harris.

Altogether there were 4,779 sera without data indicative of syphilis. Among them were 4,685 (98.03 per cent) giving identical reactions to the four tests, 28 positive and 4,657 negative. Among the remaining 94 sera (1.97 per cent.) with conflicting results there were 18 positive to the Harris. Half of these sera with conflicting results were positive to only one test, which in 6 cases was the Harris.

Among the 4,779 sera without syphilis data there were

46 positive (or doubtful) to the Harris (0.96 per cent.)

79 positive (or doubtful) to the Bordet-Wassermann (1.65 per cent.),

62 positive (or doubtful) to the Kahn (1.30 per cent.),

82 positive (or doubtful) to the Meinicke (1.72 per cent.)

**Comparison of the Strength of the Harris Slide Test with that of the Other Tests (Table VI)**—The syphilitic sera giving a definite positive or a weak positive reaction to all the tests, or a negative reaction to all, were therefore classed as identical results. Among these sera there were more which gave markedly positive reactions to the Bordet-Wassermann and to the Meinicke than to the Harris and the Kahn. When there was a conflict of the reactions in sera from patients with a history of syphilis, Meinicke's was the test which yielded the greatest number of definitely positive results whereas here also the Harris occupied third place among the four tests.

TABLE V

COMPARISON OF THE HARRIS SLIDE TEST WITH THE THREE OTHER REACTIONS IN SERA WITH NO EVIDENCE OF SYPHILIS

Sera from	No of sera	Identical results				Conflicting results		
		No of sera	—	—	No of sera	Number of positive reactions		
						3	2	1
Pregnancy	1,544	1,529	10	1,519	15	3	1	11 (2)
No diseases	530	526	—	526	4	—	1 (1)	3
Diseases of the respiratory tract	228	221	4	217	7	3 (2)	3 (1)	1
Acute infections	185	181	1	180	4	1	1 (1)	2
Various other diseases	2,033	1,980	1	1,979	53	6 (2)	23 (3)	24 (2)
No notes	259	248	12	236	11	3 (2)	2	6 (2)
Totals	4,779	4,685	28	4,657	94	16 (6)	31 (6)	47 (6)

( )—Number of positive Harris Slide Tests



TABLE VI  
STRENGTH OF REACTION IN THE VARIOUS TESTS

Methods	Identical results			Conflicting results			
	+	±	—	+	±	—	
Harris	281	45	301	37	28	85	Evidence of syphilis
B-W R	308	18	301	49	15	86	
Kahn	276	50	301	34	30	86	
Meincke	300	26	301	85	23	42	
Harris	22	6	4,657	9	9	76	No evidence of syphilis
B-W R	27	1	4,657	37	14	43	
Kahn	21	7	4,657	15	19	60	
Meincke	21	7	4,657	40	14	40	

Altogether among the syphilitic sera there were 318 giving a definitely positive reaction and 73 a weakly positive reaction to the Harris, whereas the corresponding figures for the Meincke were 385 and 49, for the Bordet-Wassermann 357 and 33, and for the Kahn 310 and 80 respectively

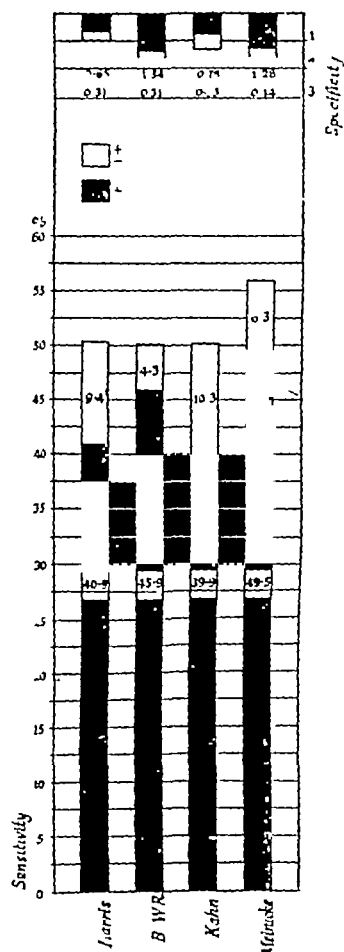
Among sera without syphilis data there were 31 giving a definitely positive reaction and 15 a weakly positive reaction to the Harris, whereas the corresponding figures for the Kahn were 36 and 26, for the Meincke 61 and 21, and for the Bordet-Wassermann 64 and 15 respectively. As pertinent data were either defective or, in the case of 259 sera, altogether lacking, there may have been some syphilitic sera among them. Even though this is a possibility, the specificity of the Harris test must be considered to be very satisfactory.

The sensitivity and specificity of each reaction is shown in the graph.

### Discussion

The comparative investigations of the Harris slide test and the three other syphilis tests carried out as a matter of routine at Gade's Institute on current material has shown that the former possesses a sensitivity on a level with that of the Kahn standard test and the Bordet-Wassermann test, whereas the Meincke clarification test has yielded a greater number of positive results. If, however, a distinction is made between definite and weak positive results, the Bordet-Wassermann test also gives a greater number of definite positive results than the Harris slide test, while the Kahn standard test is at about the same level with it.

In a preliminary report on the test, Harris



GRAPH—Sensitivity and specificity of Harris, Bordet-Wassermann, Kahn, and Meincke reactions

and others (1946) recommended microscopic readings at a hundred times magnification. We adopted this microscopic system in our preliminary investigations, which ante dated the investigations reported in this communication, but we found that it was difficult in several sera to decide whether the reaction was negative or weakly positive, as there was in these sera a "roughness" difficult to distinguish from small clumps. Accordingly, we read off the results with a lens immediately after rotation. We found this procedure satisfactory, it is easier and quicker than a microscopic reading. It is, however, possible that we recorded as weakly positive sera which on a microscopic reading would have been read off as definitely positive. As, however, we have found that what is most important is to distinguish between negative and weakly positive results, we have continued to use a lens and have thereby achieved results with satisfactory sensitivity and very good specificity.

The reading itself, as practised in our laboratory, is therefore easy and only to a slight degree dependent on a personal opinion in borderline cases. Most of the definitely positive results are also directly visible to the naked eye.

Except in Oslo, Norway is equipped with few laboratories which undertake diagnostic serological reactions in syphilis, and the lines of communication are still in many places so defective that samples of blood take several days to reach this laboratory. Hence a discussion of the possibility that the various hospitals lacking laboratories for the serological diagnosis of syphilis could profitably undertake a simple serological test for syphilis with good sensitivity and specificity as a routine measure. They would thus have to send to a special serological laboratory only those sera which gave a positive or questionable reaction to such a test. This would, however, be a retrograde step in the serological study of syphilis.

At most laboratories it is now the custom to carry out several diagnostic serological syphilis reactions side by side. These reactions supplement one another, and thus make a diagnosis more certain than when it depends on only one reaction. Hitherto no reaction has been devised which is so pre-eminent that it renders all other reactions superfluous. There are plenty of examples showing that even the

most delicate reaction can fail to indicate definite cases of syphilis when other reactions, in other respects found to be less delicate, have been positive.

The need for blood donors has of late years constantly grown. But there are many examples of infection with syphilis by blood transfusion. The serological examination of blood donors for syphilis before a blood transfusion has, therefore, been adopted as a routine measure. This examination should include several syphilis reactions, but when the same donor is used at intervals of only a few months, and it is not possible on each occasion to undertake a complete serological examination for syphilis at a laboratory it would be better to carry out a single reaction than to omit it. Under such conditions the Harris slide test, with its simple and rapid technique, should prove useful provided it is undertaken by a serological expert.

#### Conclusion

The Harris slide test is useful in the diagnosis of syphilis.

After comparative investigations with the Bordet-Wassermann reaction, the Kahn standard test, and the Meinicke clarification test in 5,556 sera, we have found the sensitivity of the Harris test satisfactory and its specificity good.

The antigen in the Harris slide test consists of chemically pure lipoids. All the test solutions are standardized. The test is rapid and easily carried out. It is easy to read off the results, and only in a few doubtful cases must personal judgment be depended on.

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# BEHCET'S SYNDROME

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The literature on Behcet's Syndrome has been reviewed by Curth in America (1946), Katzenellenbogen (1946), and Ephraim (1944) in Palestine, and in this country by Prosser Thomas (1947). Though cases of this kind were described by several authors before Behcet, he was, nevertheless, the first to recognize the clinical unity in one patient of the three cardinal symptoms, and he called it the triple-symptom complex (Behcet, 1937).

The reported instances of the fully developed syndrome are not many, but since the diversity of the presenting symptoms must have led many patients to various medical specialists, it is likely that many cases have been reported under the symptoms and signs pertaining to the system in which the specialist in question was most interested. The fully developed disease presents oral and genital ulcers with various, sometimes grave, eye lesions. These signs may appear simultaneously or successively in any order, e.g. with lag periods of up to twenty-one years between the ulcers and the eye lesions (Whitwell's case, 1934), and may be of any degree of severity. Recurrences are frequent, but without predictable regularity. Single attacks have occurred, although the possibility of late recurrences must be remembered in prognosis. None of the lesions by themselves are sufficiently diagnostic—but the combination of two or three symptoms in the course of one attack or as recurrences may give a fairly sure indication of "Behcet's syndrome".

## Case Reports

The obscure aetiology may justify the following notes on two cases referred to

venereal disease and skin departments of a military hospital as ? secondary syphilis and ? Vincent's stomatitis respectively.

## CASE 1

A cadet, aged 18, single, was referred to a venereal centre by his medical officer with the diagnosis of ? secondary syphilis.

*On admission*—A healthy man had had painful ulcers of mouth and penis for one week, he denied sexual intercourse. There had been no previous major illnesses, and in particular no indication of previous venereal disease, skin disease, or aphthosis.

*Examination*—There were small, shallow ulcers in the mouth, especially the inside of the lips. Tonsils, teeth, and gums appeared healthy. There were similar ulcers on the glans penis and sulcus coronae. Dark-ground examination for *T. pallidum* gave negative results. Direct smears and cultures from the lesions showed no pathogens. Kahn, Wassermann, and gonococcal complement fixation tests were all negative, and there was no pyrexia.

*Progress*—Two days after admission the patient developed bilateral conjunctivitis and ciliary injection. No pathogenic organisms were found in the conjunctival secretions. The eyes were improving slowly after a week, when he developed pyrexia of 103° F and complained of pain in his nose. An early furuncle was found in his nasal passage, and soon afterwards he began to have oedema of the face. The ulcers of mouth and penis began to show signs of regression (two and a half weeks after their first appearance). He was given three-hourly intramuscular injections of 20,000 units of penicillin for his furuncle, which burst shortly afterwards with subsequent disappearance of the constitutional symptoms. Smears and cultures from the nasal boil showed *Staph aureus*.

The oral and penile ulcers had maintained their improvement in the meantime, and the eyes were almost entirely clear, but one gained the impression that the course of penicillin had not contributed to this event as the regression had started before penicillin therapy and had progressed very slowly during treatment. The patient was discharged to duty four weeks after admission.

#### CASE 2

A lance-corporal, aged 30 married, was admitted to a venereal disease and skin department with a history of ulcers in the mouth. These had started a week before as small erosions and became painful as they progressed. He was treated by his medical officer and a dental surgeon, but the condition became worse. A provisional diagnosis of Vincent's stomatitis was made.

*On admission*—The man was very depressed and pale, with painful sores in his mouth. There was nothing relevant in his personal medical history, and no tuberculosis or allergic diathesis in the family history.

*Examination*—Widespread ulcers were seen in the patient's mouth, their average size being 2 to 4 mm with a tendency to coalesce both buccal membranes and the hard and soft palates were affected, and in particular the lower lip, which showed some oedema. There was slight cervical adenitis. Teeth, tonsils and tongue appeared healthy. There was some folliculitis on the face and shoulders.

The glans penis showed numerous discrete sores, and on the shaft were two larger deeper, and more irregularly outlined ulcers. There was no inguinal adenitis. The patient asserted that he had not noticed the genital sores until the day before admission.

Repeated dark-ground examinations were negative for *T. pallidum* and also for Vincent's spirochaetes from both sites. Repeated smears and cultures failed to show any pathogens. Weigert-stained films were searched without success for inclusion bodies. Kahn test was negative. The red blood count was 4,800,000 per 100 c.mm of blood, and the white 4,800, the differential count was normal.

*Progress*—Next morning the condition had become more painful and the patient was able to take nothing but a little fluid, the genital ulcers had increased in extent. He was now given 100 mg tablets of nicotinic acid five times a day for six days, making 3,000 mg. in all. No other treatment was given. His diet consisted of milk and later, ordinary hospital diet. After the third tablet the patient volunteered the information that the pain had almost vanished, and by next day the ulcers of mouth and genitals appeared to be healing. His mental attitude was euphoric, in

great contrast to his former dejection. On the fourth day of treatment there were only dusky areas to indicate the former sites of ulcers. A few days later he was discharged and was asked to report any recurrence of symptoms but he has not done so yet.

#### Discussion of Cases

The first patient showed the triad of stomatitis, genital ulcers, and eye lesions (conjunctivitis and mild iritis), which is characteristic of the fully developed Behcet's triple-syndrome complex. In addition there was the intercurrent furunculosis, a feature often noted in this condition.

The second case was an incomplete form of the same disease. Similar "formes frustes" have been described previously (Whitwell, 1934, Popoff, 1938, O'Leary, 1933, Michaelis, 1937, Gray, 1924, Berlin 1944) and appear to be more common than the fully developed triad.

#### Diagnosis

It is not necessary to wait for recurrences before a diagnosis is established, as single attacks of the disease are well known (Pils, 1925 Kumer, 1930, Talalov, 1934, Carol and Ruys, 1928, Chauffard and others, 1923).

Combinations of two symptoms of the triad, such as oculo-genital and oculo-oral have been observed by Blobner (1937), Cavaia (1940), and Franceschetti and Valerio (1940). In our present state of knowledge any two symptoms of the triad are the minimum needed to make a diagnosis, thus recurrent or single aphthosis of mouth or genitals or non-specific irido-cyclitis by themselves are insufficient, nor is there any specific laboratory or therapeutic test known to aid in diagnosis.

#### Treatment

All treatments, including administration of penicillin and sulphonamide compounds, have failed, only two patients treated by Knapp (1941) and Schultheiss-Linder (1941) with nicotinic acid, appear to have reacted promptly. Knapp's therapy had little success with other workers. Benadryl has been tried in a case of aphthosis without effect (Lynch, 1947).

#### Aetiology

Behcet's belief in a specific virus has not been confirmed nor his contention that focal sepsis plays a part in producing and

maintaining the disease Tuberculosis as an ætiological factor is now discounted (Curth, 1946) A similarity to herpes has been noted by Katzenellenbogen (1946) Allergy, particularly in connexion with the *S aureus*, is considered by Weve (1923) and Foss (1941) to play a part in causation Several authors have noted a peculiar skin sensitivity which produces reactions to all intradermal tests and has even reacted to physiological saline injections and the prick of a sterile needle Blobner (1937) likened this non-specific reactivity of the skin to the so-called "pathergy" of Urbach, which is not based on an antigen-antibody reaction Cavara (1940) believes that a virus induces sensitivity to the staphylococcus

In one necropsy on a patient who had died with progressive central nervous symptoms, perivascular round-cell infiltration of the brain was found, as well as œdema of the liver (Berlin, 1944) Liver enlargement was noted by Carol and Ruys (1928) and by Michaelis (1937) Apart from Berlin's fatal case, symptoms of the nervous system were observed by Prosser Thomas (early neuritis) and Knapp (? disseminated sclerosis) Mental depression was noted several times (as in my second patient) Arthritis was found in several cases, and chronic dysentery, ileitis, and ulcerative colitis preceded a few

It is clear from the many careful and competent laboratory investigations that no known infective agent can be held responsible for the disease Biochemical findings of the blood, urine, fæces, cerebrospinal fluid, and gastric secretions were normal The positive skin reactions to a great diversity of unrelated substances, ranging from physiological saline, tuberculin, and staphylococcus toxoid to Frei's antigen, appear to emphasize the non-specificity of the disease There is, however, a similarity between the symptom pattern of Behcet's syndrome and that of other better known diseases, and the former could be a deficiency disease In the Table the main characteristics of Behcet's disease are set out, together with those of a group of deficiency diseases

Stomatitis, eye lesions, balanitis, various skin affections, late mental symptoms, and the chronic relapsing course can be found in the Behcet syndrome groups as well as in the deficiency diseases listed It is also noteworthy

that a few of these cases were preceded by chronic bowel disorders, and that nervous symptoms did occur late in the disease, thus making for greater similarity to the deficiency diseases mentioned in the Table Moreover no causative agent of infection has been found in the triple syndrome

How may one reconcile the favourable results with nicotinic acid in Knapp's, Schultheiss-Linder's and the present second case, with the negative reports by other workers? Have different conditions been grouped under the same diagnostic heading, in which case nicotinic acid might be used as a therapeutic test aiding differentiation? Has nicotinic acid been given in too low a concentration? This is possible in the case of some workers who gave 100 to 150 mg nicotinic acid daily for a few days and recorded failure For the treatment of the mental confusion of acute nicotinic acid deficiency, Sydenstricker (1943) suggested 100 mg of nicotinic acid (or 30 mg of nicotinamide) hourly for ten doses in the first two days, then 500 mg daily for several days It might be relevant to mention the recent work by Ellinger and Benesch (1945), in which it is suggested that sulphonamide compounds destroy intestinal organisms which synthesize nicotinic acid These drugs should, therefore, not be administered concurrently There is also some evidence that a low carbohydrate intake enhances the activity of the vitamin

I am of the opinion that the variations in the symptomatology of Behcet's syndrome suggest various deficiency factors, but that the general picture fits well within the frame of the complex syndromes of avitaminosis B Secondary invasion by organisms, in particular the staphylococcus, modifies the clinical picture

### Summary

Two cases of Behcet's triple syndrome are described One patient conformed to the classical description of the disease, the other showed severe oral and genital ulceration and was considered to have the incomplete form of the same syndrome

Ætiology is discussed, neither infection nor allergy is thought to be the primary cause Deficiency disease (vitamin B complex) is suggested

TABLE  
COMPARES BEHCET'S SYNDROME WITH AVITAMINOSIS 11

Disease	Signs	Associated Signs	Course	Aetiology	Treatment
Behcet's Syndrome (full)	Recurrent genital ulcers, stomatitis, eye lesions	Non specific skin sensitivity, pyoderma, acne, erythema nodosum, Arthritis, colitis, dysentery. Various nervous disturbances	Chronic with recurrences. May lead to blindness and encephalopathy		As above
(incomplete)	Any two of the above	Milder often less complicated	Often single attack		As above
Pellagra	Recurrent stomatitis, dermatitis, and diarrhoea	Amblyopia and atrophic gastritis. Previous disease of alimentary tract associated	Chronic with recurrences	Deficiency of nicotinic acid and riboflavin	Reduced carbohydrate intake, large nicotinic acid and riboflavin therapy
Sprue	Recurrent stomatitis, glossitis, fatty diarrhoea, irritability and anaemia	Conjunctivitis depression. Previous disease of alimentary tract associated	Chronic, with recurrences	Deficiency of folic acid and vitamin B complex	Vitamin B complex as folic acid and liver, low fat and carbohydrate diet
Ariboflavinosis	Glossitis, cheilosis, conjunctivitis, corneal vascularization, keratitis	Seborrhoea. Often associated with sprue, pellagra etc	Chronic, with recurrences	Deficiency of vitamin B <sub>2</sub>	Massive riboflavin therapy
Diabetes Mellitus complications	Glossitis, intertrigo, pyoderma, balanitis - often mental depression		Insensitive to insulin if carbohydrates high in diet. Relieved by nicotinic acid	Deficiency of nicotinic acid (Rudy and Hoffmann 1942, Sydenstricker 1943)	Massive nicotinic acid therapy and low carbohydrate diet.

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# THE EFFECTS OF SYRINGE-TRANSMITTED JAUNDICE ON THE OUTCOME OF THE TREATMENT OF EARLY SYPHILIS

BY

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During the world war 1939-45 the incidence of post-arsphenamine hepatitis in many military and other venereal diseases clinics reached a very high percentage, in some centres up to fifty per cent of cases. Observations by Bigger (1943) and MacCallum (1943), and large-scale experiments by Salaman and others (1944) and by Laird (1946), indicated that this disease was transmitted as a result of inadequate sterilization of syringes. Much has been written about the effect of jaundice on the patient, but little has so far been said about its result on the prognosis of the syphilitic infection under treatment.

## The Present Study

This study is an analysis of case records of 556 male patients suffering from primary or secondary syphilis and observed at a hospital where this form of jaundice was particularly high. All patients began treatment on the four-course arsenic and bismuth schedule then in vogue. This consisted essentially of four courses of ten weekly injections to a total of 585 g. of neoarsphenamine and 20 g. of bismuth per course. There was usually a short initial period when the injections were given twice weekly, and a rest of one month was allowed between courses. The total length of treatment for an uncomplicated case was one year. Penicillin therapy was introduced during the time that many of the patients were under review, and a proportion of them received penicillin after one or more courses had been given in lieu of the remainder of the treatment. In these cases, commercial penicillin in aqueous solution, which may have contained from 10-40 per cent. of penicillin K

was used in sixty three-hourly injections to a total of 2.4 million units.

Of the 556 patients 278 developed jaundice and 278 did not. This exact splitting into two equal groups was coincidental and not arranged in any way. The average age of all patients was 29.28 years, and there was no significant difference of age in the two groups. Of the jaundiced patients, 199 received 'long-term' treatment with bismuth and arsenic throughout, and 79 had their treatment curtailed by the substitution by penicillin. Of the non-jaundiced patients 61 had the abbreviated treatment with penicillin and 217 received arsenic and bismuth only. The stage of the syphilis of the patients in the two groups is shown in Table I.

TABLE I  
STAGE OF SYPHILIS IN JAUNDICED AND NON  
JAUNDICED PATIENTS

Diagnostic Stage	Jaundice	No jaundice	Total	Per cent
Sero-negative primary	104	91	195	35.1
Sero-positive primary	124	141	265	47.7
Secondary syphilis	50	46	96	17.2
Totals	278	278	556	100.0

These cases formed a large part of the investigations by Beattie and Marshall (1944) who indicated that the usual incubation period of the jaundice was 80 to 100 days. Of the 278 patients, 25 had had less than one course



of treatment, 176 between one and two courses, 46 between two and three courses, 19 between three and four, and 12 more than four courses of treatment. Not all cases, however, commenced treatment at this clinic. The average amount and the duration of the treatment given is shown in Table II.

TABLE II  
AVERAGE AMOUNT AND DURATION OF TREATMENT

Type of treatment	Average duration of treatment in months		Average amount of arsenic in g		Average amount of bismuth in g	
	Jaundice	No jaundice	Jaundice	No jaundice	Jaundice	No jaundice
Long-term	16 02	14 06	16 82	20 77	10 31	8 60
Short-term	11 55	7 46	8 75	10 11	6 60	4 30

It will be observed that the patients who did not develop jaundice received on an average 3.95 g. more of arsenic and 1.71 g. less of bismuth on the long-term schedule, and 1.36 g. more arsenic and 2.30 g. less of bismuth with the curtailed treatment combined with penicillin, than did those patients who contracted the disease. Moreover, the jaundiced patients were actually under treatment for an average of two and four months longer than the non-jaundiced patients in the longer and shorter schedules respectively.

**Toxic Effects.**—Seven patients of the jaundice group and six of the non-jaundice group developed bismuth stomatitis, while, of the complications other than jaundice due to arsenic (necessitating permanent stoppage of the drug), there were 12 in the former and 15 in the latter group. These included 21 cases of arsenical dermatitis, 4 of nitritoid crises, 1 of severe herpes zoster, and 1 of severe "ninth day erythema". There was thus no evidence that susceptibility to hepatitis means an increased susceptibility to the other complications of arsenic and bismuth. However, when these complications were grouped according to whether the patients had received the long- or the short-term treatment, it was found that the extra one and a half to two courses of arsenic given in the long-term schedule made little difference to the incidence

(19, or 4.57 per cent, occurring in the 416 patients treated on the long term schedule, and 8, or 5.71 per cent, in the 140 patients by the shortened treatment with penicillin). The incidence of bismuth stomatitis, however, was substantially reduced on the latter treatment there being only one case, or 0.71 per cent, as compared with 12 cases, or 2.88 per cent, with the former. The default rate, too, was lower with the shorter treatment, a point that has to be weighed in the balance in considering the slightly inferior results.

When jaundice developed it was the practice to admit the patient to hospital until he recovered, which process took an average of one month, no more arsenic was administered until three months had elapsed following discharge, though bismuth therapy was not interrupted. There were no deaths in this series, but one case developed ascites, and subsequent liver punctures showed a marked cirrhosis of the liver. Details of this case have been described by Dible and others (1943). Three years later this patient is still alive and apparently well. In spite of the resumption of the arsenic, only in six instances (2.1 per cent) was there a second attack of jaundice arising between two and fourteen months after the first.

**Decline to Sero-negativity.**—Tests of the blood sera were performed at the onset and before any subsequent courses of treatment. Of 361 cases of both groups which were sero-positive at the commencement, 261 (72.3 per cent) were sero-negative at the end of the first course, 85.6 per cent at the end of the second, 92.25 per cent at the end of the third, 95.02 per cent at the end of the fourth, and a further 0.55 per cent after the fourth course. 16 cases (4.43 per cent) were resistant. There was no significant difference in the rate of decline to sero-negativity in the jaundiced and non-jaundiced cases, and the numbers ultimately sero-resistant were equal, being eight in each series (2.87 per cent).

**The Follow up.**—At the conclusion of treatment it was customary to perform quarterly serological tests for one year followed by six-monthly tests for a further year during which time a cerebrospinal fluid examination was made. The European war ended and demobilization began while many of these patients were still under observation, even so, 71 per cent. were followed for six, 54.5 per cent

for nine, and 42.3 per cent. for twelve or more months after the conclusion of treatment. There was no appreciable difference in the success of the follow-up in the jaundiced and non-jaundiced group. The numbers of jaundice cases followed for six, nine, and twelve months were 197, 152, and 112 respectively, while for the non-jaundice cases the figures were 199, 151, and 123.

**The Failures.**—The accident of acquiring hepatitis made no difference to the possibility of sero-resistance, nor to the incidence of relapse. There were 12 relapses (4.32 per cent.) in the non-jaundice group, and only 9 (3.24 per cent.) in those who had had jaundice. Of the 21 relapses, there were 3 with dark-field positive lesions, 2 with a positive serological reaction at five and seven months respectively, and 1 with a negative at fifteen months. Two suffered neurological relapse, 1 of asymptomatic neurosyphilis at ten, and 1 of symptomatic neurosyphilis at fifteen months. The remaining 16 were serological relapses, occurring in 3 at three months, in 2 at six, in 5 at nine, and in 6 at the twelfth month of surveillance. These figures must be correlated with the fact that only 42.3 per cent. were actually followed for the year.

There were thus 37 failures, 17 (8 resistant and 9 relapses) in the jaundiced group, and 20 (8 resistant and 12 relapses) in the non-jaundiced group. There was no evidence that these patients received less treatment than the average of the groups from which they arose. Only in 1 had there been any severe arsenical complication (dermatitis) although 4 developed bismuth stomatitis. Only 4 had intervals of default exceeding three months, which was comparable in proportion to the series as a whole. Fourteen of the relapses occurred in the 416 patients treated on the long-term schedule (3.37 per cent.), while there was a slightly greater ratio, 7 in 140 cases, in those treated on the shorter schedule with penicillin (5 per cent.).

One of the failures was particularly disturbing. The case was that of a man aged 36 who was treated in February, 1944, for secondary syphilis. He had no jaundice or other complication before the four courses had been completed in March, 1945. His blood had become negative after the first course and remained so subsequently and was still negative one month after completion, at which stage he was demobilized. It was learnt fifteen

months later that he was in a civilian hospital with Erb's spastic paraplegia and strongly positive serological and cerebrospinal fluid findings.

Of the 37 failures, 3 arose from the 195 sero-negative primary cases (1.54 per cent.), 16 from the 265 sero-positive primary cases (6.04 per cent.), and 18 from the 96 secondary cases (18.74 per cent.). The proportion of failures, therefore, increased according to the duration of the syphilitic infection before treatment.

### Summary and Conclusions

Two hundred and seventy-eight cases of early syphilis developing syringe-transmitted hepatitis are contrasted with 278 patients who received similar treatment in the same clinic but did not develop jaundice. It was coincidental that the two groups are of equal number.

The jaundice cases received less arsenic but more bismuth, and were under treatment for a longer time than the non-jaundice cases.

There was no difference in the incidence of other toxic manifestations in the two groups, although the incidence of bismuth stomatitis was lower, while the complications due to arsenic were not reduced when penicillin was combined with a smaller amount of arsenic and bismuth.

Of the cases followed, the numbers showing sero-resistance were equal in the two groups though in this series there was actually a slight increase in the numbers of relapses in the non-jaundiced as compared with the jaundiced cases.

It would, therefore, appear that whatever the results on the life span of the unfortunately large number of patients who developed hepatitis while under anti-syphilitic treatment, at any rate the outcome of the treatment given for early syphilis is not prejudiced.

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# A RAPID METHOD OF STANDARDIZATION OF THE SHEEP-CELL SUSPENSION USED IN THE HARRISON-WYLER WASSERMANN TECHNIQUE

BY .

I N ORPWOOD PRICE and A E WILKINSON

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In reactions such as the Wassermann, in which several biological components interact, it is desirable that each reagent employed should be standardized as far as possible so that the test can be carried out under conditions which can be reproduced from day to day

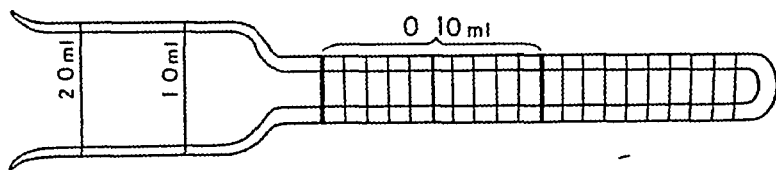
In his description of the Harrison-Wyler Wassermann technique, Wyler (1929) recommended standardization of the sheep-cell suspension by means of hæmoglobin estimations. This is done on a concentrated suspension which is subsequently diluted down to the appropriate density. This method is time-consuming in that several estimations may have to be carried out before an exact match can be obtained. Sensitization of red cells by hæmolytic immune body is a phenomenon which occurs at the cell surface, but the hæmoglobin concentration does not give a measure of the total surface area available to the amboceptor. A more accurate estimate of this area may be obtained by measuring the packed-cell volume by means of a hæmatocrit, and this forms the basis of the method described.

The sheep cells are centrifuged, the deposit re-suspended in about four times the volume of 0.85 per cent saline, and spun, the washing and spinning being repeated a minimum of four times, or until the supernatant fluid is perfectly clear and colourless. An approximately 6 per cent suspension of the packed cells is made in 0.85 per cent saline and exactly 10 ml transferred to the hæmatocrit tube with a 1 ml graduated pipette. The bulb of the hæmatocrit\* has a capacity of 2.0 ml, and the stem 0.2 ml graduated in divisions

of 0.01 ml. It is centrifuged for ten minutes at a speed of 2,500 revolutions per minute, which, with the instrument in use, has been found to pack the cells to a constant volume. The height of the column of packed cells is read off, and by simple proportion the factor for dilution of the original 6 per cent suspension to any desired density is obtained. In this laboratory a packed cell volume of 0.05 ml is taken as the standard. The calculation is shown most easily by an actual example

6% suspension—packed cell volume	0.057 ml
Required packed cell volume	0.050 ml
Dilution factor	$\frac{0.057}{0.050}$
	1.14

that is 0.14 ml saline should be added to each 10 ml of the original 6 per cent cell suspension



Equal volumes of the standardized suspension, and 0.85 per cent saline containing 12 M.H.D. amboceptor per unit volume are mixed, shaken vigorously, and then placed in a 37° C water bath. A current of air is drawn through the mixture for thirty minutes by means of a water pump. This keeps the suspension in a state of continuous agitation and ensures even sensitization of the cells. The final concentration of the cells in the sensitized suspension is approximately 2.5 per cent, and it contains an average of 600,000 cells per c.mm. The method described has been used in this laboratory for six months and it has given consistently reliable results.

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\* The hæmatocrit tube was made for us by Messrs R. B. Turner and Co., Ltd. London

# ADVERTISEMENTS ON THE TREATMENT OF VENEREAL DISEASES IN THE EIGHTEENTH AND NINETEENTH CENTURIES

Dr A. Fessler, Venereal Diseases Officer, Lancashire County Council, and Mr R Sharpe France, the County Archivist, have found in some old newspapers deposited in the County Archives at Preston a number of interesting advertisements dealing with the treatment of venereal diseases. These are somewhat similar to the leaflets published in an article by Dr Fessler in this *Journal* in June, 1946, page 85, but they cover a longer period of time, and Dr Fessler draws attention to the changing attitudes towards this group of diseases as reflected in the terminology used. In the advertisements of the eighteenth century, for example, syphilis is named and terms such as "Claps and French illness" are used. A change of outlook is shown in an advertisement of a later period, where venereal diseases are now named as 'certain diseases'. The names of the various venereal diseases reappear in the thirties of the last century.

Dr Fessler writes: 'The number of advertisements dealing with venereal diseases is small compared with advertisements dealing with other diseases. I can find only two advertisements dealing with the treatment of gonorrhoea, one of which is quack treatment at its worst, suggesting cubebs with sarsaparilla for the treatment of gonorrhoea as well as for syphilis. Another advertisement suggests the use of soap as a preventative, but this has no signature and seems to have been inserted by a soap manufacturer.'

It is interesting to note that venereal diseases must have been prevalent to a certain extent in the provinces, not only in industrial and mining areas, such as Blackburn and Wigan, but even in typical rural areas, such as Lancaster and Kendal, at the beginning of the nineteenth century, probably as a result of the Napoleonic wars."

## Eighteenth Century Advertisements

The following advertisement is from the *London Evening Post* of Feb 19-22, 1732.

D

## ANTI-SYPHILICON

The only short and most infallible CURE in the Universe for the Venereal Disease from the slightest Infection to the most extreme and deplorable Degree of it even when the Blood and Juices are thoroughly contaminated with its malignant Virus and the very Bones are affected with it.

Fresh Infections, call'd Claps, with all their attendant Symptoms, tho' ever so severe are entirely carried off by it in a few days and so as effectually to prevent the Blood and Juices from being tainted with any remaining Relicks on one Hand, or a seminal Gleet or Weakness to happen on the other.

And the most inveterate Degree of the French Illness attended with Nocturnal Pains, universal Breakings out, and all other the most exasperated Symptoms are soon overcome by it, and effectually and much more safely cured than by Salivation, Inunction or any other Method whatever and in so easy and pleasant a Manner, without impairing Strength, or occasioning Inconvenience as loudly to bespeak it the only apposite Remedy or true Venereal Antidote in the World, and this some Thousands have to their great Joy experienced.

It is pleasant to take occasions no Sickness or Disorder nor requires Confinement but may be taken and the Cure be accomplished without the Knowledge of the nearest Friend.

Those who suspect they have received an Injury may by only a Dose or two of it, be perfectly freed from all Apprehensions for it suffers no lurking Venom to lie hid in the Body but wholly extirpates it Root and Branch, in a gentle, easy and most effectual Manner.

All such likewise as doubt they have some remaining Relicks of former Injuries, may by a few Doses of it intirely free themselves from all Suspicions of that Kind, for it admits of no Foulness Corruption or Putrefaction whatever to remain in the Fluids, or to adhere to the Solids and on that Account, in all scorbutick scrophulous and even Leprous Eruptions or Foulnesses of the Skin, Glandulous Swellings and Impurities of the Juices it does more by one Dose than any other Medicine yet known can by ten.

The Price of this most noble Anti Syphilicon is but Six Shillings a Pot which considering its

# CHANCER OF THE TONGUE TWO CASE REPORTS

BY

N V RAO,

*Adviser in Venereology, S E A L F*

## Case Report, 1

An Indian NCO was transferred to the venereal disease clinic at 93 I G H (C) S E A C , on Aug 8, 1946, with a sore which he had for one month on the dorsum of the tongue. The blood Kahn test was positive. He denied any exposure or perverted sexual acts.

In March, 1946, this man had had sero-negative primary syphilis, the penile lesions were located at 10 and 12 o'clock in the coronal sulcus. He had been treated with penicillin (60 injections of 40,000 units each). The sore had healed, and he had been discharged for routine surveillance.

On admission in August, 1946, he presented a circular (1 in in diameter) indurated sore, raw, ham in colour, situated on the centre of the dorsum of the tongue (Fig 1). No slough was present. Submaxillary and submental glands were palpable, and there was a macular rash over the trunk with scattered papules, there were moist papular syphilides on the scrotum. No mucous membrane lesion was present on lips, cheeks, or fauces. Numerous typical treponema pallida were found in the secretion from the ulcer in the tongue. There were indurated scars in the coronal sulcus at 10 and 12 o'clock, but no active penile lesions. Inguinal glands were palpable, discrete, and painless. No active penile sore or urethral discharge was present.

This case, originally one of sero-negative primary syphilis with penile lesions, reported with an ulcer on the dorsum of the tongue four months after the penicillin therapy. The ulcer had the clinical characteristics of a primary chancre. Taking into consideration the clinical features and the presence of

numerous *T pallida*, a diagnosis of chancre of the dorsum of the tongue was made, although it is realized that a gumma is the most common lesion in that situation.

Another interesting feature in this case was that it looked very much like a case of reinfection, the reasons for such an assumption being (1) previous sero-negative primary syphilis with penile lesions, (2) the location of the present chancre in an entirely different position.

## Case Report, 2

A British NCO reported on Sept 20, 1946, having had an ulcer on the dorsum of the tongue for four days. He gave a history of exposure two weeks previously, the woman being a prostitute. A condom and an E T packet were used as prophylaxis. He denied any perverted sexual act. There was no previous history of venereal disease.

On examination a hard, raised, fissured ulcer was seen in the middle of the dorsum of the tongue (Fig 2). The cervical glands were palpable, discrete, and painless. No skin or mucous membrane lesion was seen. There was no penile lesion present, nor any urethral discharge. *T pallida* were found in the secretion from the lingual ulcer. The Kahn test was positive. On treatment with penicillin, arsenic, and bismuth the sore healed. The patient was discharged for surveillance on Oct 18, 1946.

I am grateful to Colonel J. L. O'Neill, IMS/1 A M C O C., 93 I G H (C) SEAC, for permitting me to publish these cases.



FIG 1—Sore on tongue, case 1



FIG 2—Fissured ulcer on tongue, case 2

## CORRESPONDENCE

*Letters are welcome on all matters of general interest. Publication does not necessarily imply that the Editor agrees with the views expressed.*

### A SPECIAL QUALIFICATION IN VENEREOLGY

Sir—Advertisements in the medical press for medical officers for venereal disease clinics reveal marked differences in the professional qualifications required. For example, one recent advertisement stipulated an M R C P or F R C S as essential while in other cases a higher medical qualification has been required, or it has been indicated that the possession of a D P H or other additional qualification would be an advantage.

These varying requirements reflect the views of employing authorities—whether voluntary hospital or health department.

The statutory requirements for a venereal disease medical officer, as laid down in the Local Government (Qualifications of Medical Officers and Health Visitors) Regulations 1930, are not expressly demanded in all cases as a necessary prerequisite to appointment. Indeed, it is by no means unknown for a medical officer to whom the conduct of a venereal disease clinic has been entrusted to attend the nearest large centre and obtain this qualification while actually conducting his own clinics.

Higher qualifications are proof of postgraduate study but except in those in which venereal diseases may be professed as the major subject do not necessarily imply any deep knowledge of venereology. The present-day C P H and D P H courses do not make any detailed study of this subject.

The statutory requirements referred to above can at most mean a reasonable primary training for the rare enthusiasts who can learn enough to make their own future experience. The majority, however, request the certificate as an additional lever for public health appointments after expiration of the 130 hours without having made any serious attempt to acquire reasonable basic knowledge.

In the case of Service specialists a very wide experience of recent infections may be obtained but they do not have to deal with many of the manifestations and problems commonly encountered in civilian clinics.

The absence in venereology of any recognized postgraduate qualification comparable to those available in other specialities and the low official standards have contributed to the belief that venereology is not a speciality. It is regarded as an unimportant side line and often made the stipendary prerogative of the junior surgeon, physician, etc. or allocated to the junior assistant medical officer of health.

This position, which would not be tolerated in other departments, has been permitted to obtain too long by venereologists who have not sufficiently emphasized the scope and importance of their speciality and insisted upon adequate training and status before responsibility is taken.

It is the duty of venereologists to secure for the medical services of the country competently trained persons to carry out this work in the best interests of the community. It is conceded that

in many venereal disease departments a consistently high standard is maintained, but in others this has not yet been achieved. The isolated lot of the part-time one-man clinic is admittedly difficult, there is often no possibility of easy consultation over clinical or sociological problems. Attendance at meetings of the Medical Society for the Study of Venereal Diseases is often impossible because of clinic times, or is not encouraged by the employing authority and, at best, is left as a non-official expense and enthusiasm. It is hoped that under the new Health Service these matters may be remedied.

The lack of a special diploma or other instrument indicating a specialist status in venereology has contributed materially to the present unhappy position. That the number of venereologists is relatively small, if we consider only those whose primary appointments lie in this field, must no longer be the excuse for apathy.

What are the possible courses of remedial action? These are (a) the institution of a diploma in venereology to be granted by an established examining body, (b) the creation of two classes of membership of the Medical Society for the Study of Venereal Diseases (possible alteration of its title to Association/Society of Venereologists and MSSVD), namely, a junior associate-membership equivalent to the present membership, and a senior Diplomate Fellowship, by examination, or (c) the formation of a Faculty of Venereologists outside the structure of, but of necessity integrated with the MSSVD, the diploma of Fellowship of which would indicate approbation as a specialist.

An additional cogent reason advanced by Mr A. J. King (personal communication) is the desire of 'the constant stream of overseas postgraduates who always enquire about the possibility of a specialist's qualification in these subjects. Naturally they wish to achieve such a qualification as evidence of the good work they have done over here'.

The standard of professional attainment envisaged would be equal for the diploma or for either fellowship. The first course offers certain obvious advantages—a diploma obtained by examination, conducted by an established examining body with the prestige of its long traditions, would more immediately be recognized and accepted as indubitable evidence of professional attainment in venereology by those authorities seeking to fill appointments.

Either of the other courses of action might in practice be easier to institute, but the principal disadvantage is that, while the professional standard exacted would be equally high, there would undoubtedly be a greater time lag before the value of the qualification was accorded full recognition.

That there is a multiplicity of special diplomas only indicates that other specialities have realized their value in securing and maintaining high standards.

The Medical Society for the Study of Venereal Diseases has long existed to encourage the "study" of the venereal diseases. It is not too much to expect this, the proper, and in fact the only, body representative of venereologists in this country to concern itself actively with the formulation of some generally accepted standard of proficiency in this work. The demand for a special *ad hoc* postgraduate qualification in venereology by the members of this society would give their council a mandate for urgent action.

To those already established and recognized, such a diploma can only mean 'an additional qualification,' to future aspirants in venereology it will be the hall mark of specialization.

We are, etc.,

A E W McLACHLAN  
DONALD D BROWN

Bristol July 1947

## BOOK REVIEWS

### TREPONEMATOSIS

By Ellis H Hudson,  
edited by Henry A Christian

(Oxford Medical Publications 1947 Pp 122)  
Price 12s 6d net)

In the year 1493 a small band of men returned in triumph to Spain and reported the presence of new lands in the West, they brought with them new maps and charts, botanical and geological specimens, and a few captured Indians to show at the court of Ferdinand and Isabella. Whether or not they brought with them at the same time a new and fell disease which, in the course of a few years, was to spread to all Europe and far to the East, is

a problem which has now interested medical historians for hundreds of years.

The argument as to the responsibility of Columbus in introducing the disease to Europe is as old as the name syphilis itself, and each of the various, never conclusive, arguments advanced by the protagonists on both sides have been repeated and elaborated through the centuries. The more vocal opposers of the Columbian theory, not surprisingly perhaps from across the Atlantic, have pointed to the existence of yaws in the African native and, in drawing attention to its spread to the West, have tried to show, by attempting to prove that yaws and syphilis were the same disease, that the boot was, indeed, on the other foot.

This book may be said to bring the whole controversy up to date, although the bias is strongly on the unionist side and with it the rejection of the Columbian theory. The concept is not that yaws and syphilis are the same disease, but rather that they are different manifestations of treponematoses or the effects of *T. pallidum*. It is argued that this organism, almost as old as Man himself, probably came out of Africa in the early migrations and that this main reservoir has ever since been responsible for its flow to the different corners of the globe. The disease as it affected the African was of the yaws type, it was and still is spread by close contact and flies, under bad social conditions. Making use of the moist skin surfaces of humid climes, it is, therefore, able easily to take root in a fresh host and therefore is primarily a disease of childhood. Being a disease of the young, the girl by the time she becomes a mother is no longer infectious and hence congenital forms are rare. Without treatment and allowed to run its full course the disease has skin and bone lesions predominant in the tertiary stage, and occasional severe mutilations such as gangosa, but neurological or cardiovascular involvement is rare.

As the centuries advanced, social conditions changed. The negro taken in slavery no longer was subject to the same climatic and hygienic conditions, and the white man contracting the disease was able to do so only by sexual intercourse with the infected. Thus the stage became set for the juvenile forms to decline and venereal types with the increased risk of congenital transmission, to increase. The spirochete, no longer able to propagate its species into a fresh host, had to rely on promiscuous sexual intercourse as virtually the only means left for survival. The warm, moist skin, still prevailing at mucocutaneous junctions and certain skin sites, showed in miniature what formerly prevailed all over the body. What is more, once the organism had taken hold it was subject to all sorts of drastic medicines,unctions and injections, and therefore in time the strain became toughened and likely therefore in animal experiments, to show certain differences between that of a strain taken from a primitive native.

This change from a juvenile contact spread of the disease to the adult venereal form was not sudden and there were transitional forms. We have areas in the world even today where the disease is an accidental infection of children but climatic conditions have forced upon it a greater likeness to venereal syphilis. Examples of this are bejel, pinta and irikintja (Australian boomerang leg). History also affords instances where the venereal form has, with suitable climatic or social conditions reverted to the primitive type. For example there is sibiens, a disease of the Highlands of Scotland at the time of the Civil war, radesyge in Scandinavia in 1700, skerlijeyo in the Balkans at the end of the eighteenth century and certain manifestations of juvenile syphilis seen in Southern Russia in the nineteenth century and even occasionally still found today.

This then is the argument. To it is added the acceptance that yaws is a very ancient disease which has always been present in the Old World

but, as it was mainly of the juvenile form, it did not find a place in ancient literature as a sexual disease. When the disease became venereal it was confused with leprosy. It is scattered all over Europe and later America, primarily by the slaves, and the white man always caught yaws, never syphilis from the African. It was probably present in very early times in the Western hemisphere but there is no evidence that the natives of Haiti actually suffered from it before the arrival of Columbus. It is therefore suggested that one or more of Columbus' men may have been infected before leaving Europe and that subsequently the more courageous of the local natives became infected, in turn infecting others, and thus, in consequence, the Indies were given the blame, a pretence eagerly maintained by the Church.

This book is recommended to all those who have not yet studied this absorbing subject. For the great number who have it is a new, sober, entertaining, and constructive book which attempts perhaps only too successfully, to explain all the differences of opinion which have existed between the two sides.

(It may be churlish when this book has been found so enjoyable to point out that Prince Henry of Portugal did not reach the equator in 1470, as he had died over ten years before.) R.R.W.

#### HANDBOOK OF DIAGNOSIS AND TREATMENT OF VENEREAL DISEASES

By A. E. W. McLachlan, M.B., Ch.B. (Ed.),  
D.P.H., F.R.S.E.

(Edinburgh: E and S Livingstone, 1947. Third  
Edit. Pp. 375. Illustrated. Price 15s. net.)

The appearance since 1944 of three editions of McLachlan's *Handbook of Venereal Diseases* is almost an adequate testimony of its usefulness and popularity. The third edition, which now comprises 375 pages, has received few expansions or additions in text or illustrations. The latter, which maintain effectively the high standard achieved in previous editions, portray judiciously selected studies, twenty in colour of the more common venereal conditions.

The text on the treatment of syphilis has the advantage of not being relegated to a separate and sometimes remote chapter, as it has been in some books on this subject, but follows hard on the descriptive matter of each of the various stages of the disease—an arrangement which will be appreciated by the student while the clinical aspects are fresh in his mind.

The gradual accumulation of data on the use and results of penicillin therapy in early syphilis during the last two years has led to some expansion of the text. The amount of penicillin considered to have been possibly adequate in 1945 (2.4 mega units in 7½ days) and advocated in the previous edition has now been increased in amount to from 7.5 to 10 mega units in 15 days and in addition treatment with arsenicals and bismuth is recommended as it now is by most authorities.



Four alternative schedules of treatment with arsenicals and bismuth are advocated, including an intensive twenty-day course for in patients. In advising the use of intensive arsenical therapy more stress should be laid on the high incidence of the toxic effects of arsenic, which are an unwelcome and important accompaniment.

Arsenical dermatitis and other arsenical toxic effects are well described and illustrated, but in the section on their treatment there is no mention of the use of BAL (di-mercaptopropanol) which has recently superseded all other remedies.

The lesions and pathology of the various stages of syphilis are lucidly described, as also is the Wassermann reaction and its clinical interpretation. The use of the so-called 'provocative' Wassermann reaction is still advocated although, surely, most authorities have lost faith in this procedure, more especially since a similar 'provocative' effect was demonstrated in non-syphilitic persons by Barnett and others in 1938.

The instructions on the use of bismuth in early syphilis are given in full practical detail but are somewhat marred by the plethora of compounds listed—sixteen in all—without any clear indication of which preparations are favoured or used by the author.

The instructional value of the Handbook, in general, is high, although the text is necessarily compressed. In particular the chapters on congenital syphilis, on vulvovaginitis, and on gonococcal infections of the eye are noteworthy.

The inclusion in future editions of a summary of the present-day public health anti-venereal measures and a brief account of their aims and results would no doubt be welcome to the post-war student, who in many instances is an ex-serviceman with some interest in and knowledge of hygiene.

The Handbook will doubtless retain its position as the most useful small book on this subject for the medical student.

VEL

### PENICILLIN IN GENERAL PRACTICE

By J L Hamilton-Paterson, M D

(New York, London, and Toronto Staples Press Ltd 1947 Second Edit Pp 105, with charts and illustrations Price 5s net)

The first edition of this very useful little book was published in 1946, and so rapidly is the field of antibiotics changing its lines of development that already a second edition has appeared, bringing a variety of matters up to date.

There are some useful paragraphs on skin sensitivity and allergic reactions and their significance. Local administration by dressings and ointments and the rather newer use of finely divided sprays (areosols) are more fully discussed. The treatment of subacute bacterial endocarditis is brought up to date, and the chapter covering such miscellaneous conditions as urinary infections, the fevers, puerperal sepsis, and meningitis carries a number of new points. It is interesting to note that nowadays therapeutic concentrations of penicillin can be obtained within the eyeball, apparently without local toxic effect. The chapter on venereal

diseases is short but to the point and should remind us of the limitations as well as the success of penicillin in this sphere. On the technical side, only the briefest outline of the older laboratory methods is given, but in a work of this type more is not necessary. In that a variety of technical modifications are daily being introduced in different laboratories, this section might well have been left out altogether. There is one actual though obviously accidental omission which occurs in the table giving the sensitivity of various organisms tested in vitro, where there is no mention of the gonococcus. However, the omission in no way influences the conclusion that this little book contains a really concise and helpful review of a subject changing so rapidly. The author cannot be expected to do more than, first, carefully catalogue the facts, and then append the latest possibilities and suggestions. These tasks he has done most admirably.

F A K

### MONOGRAPHS ON THE PROGRESS OF RESEARCH IN HOLLAND MODERN DEVELOPMENTS OF CHEMOTHERAPY

By E Havinga, H W Julius, H Veldstra, and K C Winkler

(Amsterdam Elsevier Publishing Co, Inc, London Cleaver-Hume Press Ltd 1946 Pp 175 Price 15s net)

No doubt most of us have imagined that under the stress of invasion and the long hard five years of German occupation the tide of medical research in Holland would have remained at low ebb throughout that long period of suffering. It is therefore with some surprise and with much admiration that readers in Great Britain will inspect this sample of the series of monographs on the progress of Dutch research work during the world war 1939-45. *Modern Developments of Chemotherapy*, one of a series of twelve monographs on scientific subjects, is a slim, attractive volume of 175 pages, excellent as to print and general format. It tells the story in detail of wartime research by Dutch scientists on the mechanism of the action of the sulphonamides, on investigations into the synthesis and activity of new sulphanilamide derivatives, and on pharmacological studies and therapeutic results. Extensive studies are recorded of the physico-chemical characters of the sulphonamides, especially in relation to their antagonism by *p*-aminobenzoic acid and peptone. The methods of investigation included electrometric titrations, the study of ultraviolet absorption spectra, and determinations of surface activity. The behaviour of bacterial cultures in media containing sulphonamides receives detailed and extensive consideration, following which the work of Dutch scientists on the mode of action of these compounds is fully and critically discussed.

Among the many sulphonamide compounds synthesised during the German occupation are eighteen derivatives of pyrimidine, of which six

are reported to possess an anti pneumococcal activity *in vivo* which is equal to or perhaps even stronger than that of sulphapyridine. One of these derivatives, 2-sulphanilylamino-4-methylpyrimidine (known as percocside), which will be of particular interest to readers of the *Journal* is stated to have given results in the treatment of gonorrhoea which surpass those given by sulphapyridine. It is said that it has the advantage of low toxicity and that its acetyl derivative has a

greater solubility than that of acetyl-sulphapyridine.

The high quality and range of the research work done in a country cut off from all access to the help and stimulus of world literature through five long years will create unbounded admiration in the minds of all of us. The author's modest foreword to the book bears the defiantly appropriate birth-date: Amsterdam on V E Day, 8th May 1945. V E L

## ABSTRACTS

*(The abstracts are divided into the following sections: syphilis (general therapeutic pathology), gonorrhoea (general therapeutic pathology), other venereal disease conditions, public health. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.)*

### SYPHILIS (GENERAL)

A Study of Syphilis in a Negro High School in the City of Baltimore, 1939-1943 (1946) *J. Ven. Dis. Inform.*, 27, 200

This is an analysis of two serological surveys of a negro high school. In each survey one fourth of those showing positive blood reactions had been known previously to have had syphilis, while 50% of the syphilis was discovered in students under 15 years of age.

Tables were compiled to assess the probability of acquiring syphilis while at high school. In males no infections occurred between the ages of 11 and 15 years, but by the sixteenth birthday the probability of infection was 9 per 1,000, and at the age of 20 it had reached 76 per 1,000. In the females no new infections occurred between 11 and 14 years, but by the fifteenth birthday the probability rate was 24 per 1,000 and by the age of 20 as high as 170 per 1,000. Previous studies on adult negroes in this area had shown that by the age of 25 nearly 23% of males and 35% of females had become infected with syphilis.

R. R. Willcox

Asymptomatic Neurosyphilis: Prognosis. HAHN, R. D., and CLARK, E. G. (1946) *Amer. J. Syph.* 30, 513

The prognosis of asymptomatic neurosyphilis, with regard to the eventual state of the spinal fluid and to the clinical outcome, was studied in 533 patients on whom at least two cerebrospinal-fluid examinations had been done, and in 467 patients who had had at least two physical examinations

(271 male and 262 female; 191 white and 342 negro). Only 8.5% of the patients had received any treatment before the first positive spinal fluid test. Routine treatment of all cases consisted of trivalent arsenicals and bismuth. Tryparsamide or malarial therapy was also given to a small number of cases.

A large part of the report is devoted to a detailed analysis of the subsequent changes in the spinal fluid in respect of age, race, sex, duration of infection, treatment, initial change in the spinal fluid, and, in particular, the relation of spinal fluid changes to the clinical outcome. It was noted that the probability of the development of clinical neurosyphilis during the first 10 years of observation was less in the youngest group (under 25 years) than in the other age groups, presumably on account of the shorter duration of the infection. In general the more marked the pathological change in the initial spinal fluid tests the more unfavourable were the changes in the ultimate spinal fluid examination and the greater the probability of the onset of manifest neurosyphilis. Spinal fluids, initially of Group I or II, became negative in about half the patients, whereas when the initial tests showed the spinal fluid to have been of Group III type, the fluid became negative subsequently in only about a quarter of the patients.

The authors point out that the prognosis in many patients is favourable even when treatment has been totally inadequate. Adequate treatment with trivalent arsenicals and bismuth (40 or more injections of each) was of distinct value in asymptomatic neurosyphilis. No advantage seemed to have accrued from the addition of tryparsamide.

therapy Although the number of patients who received malarial therapy was small (40), it appeared to have been the most effective form of treatment

The probability of ultimately developing clinical neurosyphilis was found to be greater with increasing positivity of the spinal fluid Spinal fluids of Group I type at initial examination led to clinical neurosyphilis in 1.6% of patients at 5 years and in 7.9% at 10 years In the case of Group II fluid this probability increased to 6.5% at 5 years and 16.5% at 10 years With the paretic type of fluid—Group III—the outlook is more ominous, manifest neurosyphilis developing in 12.8% at 5 years and 21% at 10 years Accompanying graphs portray the probability of the development of parenchymatous neurosyphilis and of meningo-vascular neurosyphilis according to the degree of the positivity of the initial spinal-fluid examination The slight influence of race and sex in the prognosis of asymptomatic neurosyphilis was not thought to be of any practical importance in the management of the individual patient

V E Lloyd

### SYPHILIS (THERAPEUTIC)

#### Results of Rapid Treatment of Early Syphilis HELLER, J R (1946) *J vener Dis Inform*, 27, 217

This is a progress report on an evaluation study of the results in early syphilis of various intensive-treatment schedules, using penicillin alone or in combination with other drugs, and of certain methods and schedules of intensive treatment with arsenicals The records from 16 American rapid-treatment centres, which show the results obtained after 12 to 15 months' observation of 8,000 patients, are the basis of the study

Wide differences were noted in the effectiveness of treatment begun in the various stages of early syphilis Treatment begun in the primary stage gave better results than that begun in the secondary stage or after relapse from a previous course of intensive therapy In a series observed for 15 months after treatment there was no significant difference between the schedules using penicillin alone and those in which penicillin in smaller doses was administered in conjunction with arsenoxide There was no essential difference between results when 600,000 units of penicillin was used and when 1,200,000 or 2,400,000 units was used It would, however, seem that the effectiveness of any penicillin treatment for early syphilis is enhanced by the inclusion of bismuth There was no significant difference between results obtained from 40,000 units of penicillin administered 3-hourly for 4 days and the same dose 6-hourly for 8 days When penicillin was combined with small amounts of arsenoxide and bismuth the mortality rate was 1 in 4,312 With intensive arsenotherapy the death-rate ranged from 1 per 149 cases treated with 5-day intravenous drip to 1 per 1,873 cases treated by multiple injections

T Anwyl-Davies

#### Syphilitic Nephrosis as a Manifestation of a Renal Herxheimer Reaction following Penicillin Therapy for Early Syphilis A Case Report SCOTT, V, and CLARK, E G (1946) *Amer J Syph*, 30, 463

A case is reported of massive oedema of the legs with marked proteinuria, low plasma albumin with inversion of the albumin-globulin ratio, together with normal renal function-tests The patient, a male negro aged 31 years, had a generalized syphilitic rash and a Kahn reaction of 200 units There was no initial urinary abnormality Intramuscular penicillin therapy was begun with 30,000 units at 2-hourly intervals Six hours after the first injection the oral temperature was 39.5° C, and several injections were omitted Treatment was resumed next day when the temperature had subsided On the third day of treatment a second rise of temperature to 39.3° C was recorded, which returned to normal in 7 more days Nocturia occurred from the second day Penicillin was given to a total of 4.8 million units Five days after the end of treatment increasing swelling of the legs began, and later involved the genital and periorbital regions Urine analysis showed a heavy precipitate of protein, granular casts, and occasional leucocytes, the blood non-protein nitrogen was 15 mg per 100 ml, total serum protein was 5.9 g. % A concentration diuresis test showed concentrating ability to a specific gravity of 1.022 The excretion of phenolsulphonphthalein was 75% in 2 hours The cutaneous papules had healed When placed on a salt-free diet the patient lost 30 lb in weight in 5 days, the oedema disappeared, and the urine became free from protein On analysis 32 and 95 days later it was found to be normal

In the authors' opinion the associated early syphilis, the normal urine before treatment, the fever after the initial penicillin injections, and the nocturia, followed by the nephrotic syndrome which subsided without further antisyphilitic treatment, all suggest that the nephrosis was a focal Herxheimer reaction in the renal parenchyma

V E Lloyd

#### The Effect of Streptomycin on Experimental Syphilis Infection of Rabbits FISKEN, R A, and GRUHZIT, O M (1946) *Amer J Syph*, 30, 581

This is a report of an investigation at the Parke, Davis Research Laboratories of the possible efficacy of streptomycin in experimental syphilis in the rabbit Groups of 4 to 6 rabbits with active syphilitic lesions were treated with intravenous injections of streptomycin of 1,000, 2,000, 3,000, or 4,000 *subtilis* units per kilo, in three divided doses each day for 21 days Since this dosage was without visible effect on the lesions, the rabbits were subsequently given 6,000, 8,000, or 10,000 *subtilis* units per kilo in three divided doses each day for 13 days During the first 3 weeks some of the lesions progressed and motile spirochaetes could still be found Spread of infection to the uninoculated testis was observed in some animals In the second period of treatment the regression of

lesions was similar to that of syphilis in untreated rabbits. Spirochaetes were found in most lesions up to 12 days after the higher range of dosage. The popliteal lymph nodes, excised 6 weeks after the second treatment, were implanted into normal rabbits, all such transfers were followed by the development of lesions containing motile spirochaetes. The authors conclude that the continued administration of streptomycin does not abort syphilitic lesions or produce systemic sterilization.

V E Lloyd

**The Treatment of Experimental Syphilis with Penicillin.** CARPENTER, C M, BOAK, R A., and JACOBS, L M (1946) *NY St J Med*, 46, 2150

This report from the University of Rochester describes a prolonged series of experiments to assess the therapeutic efficacy of sodium penicillin and of penicillin fractions F, G, and X on syphilitic infection in rabbits. The authors found that penicillin is capable of curing 100% of syphilitic rabbits if it is given over a sufficiently long period, and that this time factor appears more important than heavy dosage.

Six schedules of penicillin treatment were tested (1) Single injections of sodium penicillin ranging from 2,000 to 50,000 units per kilo body weight were ineffective. (2) Two doses of 8,000 units each at a 3-hour interval were ineffective. (3) and (4) Up to 16,000 units per kilo of body weight at hourly intervals for as long as 16 hours also failed to cure. (5) Two daily injections at 8-hour intervals for 16 days, 10, 0, 0, 90, 100 and 100% respectively of the animals treated with 250, 500, 1,000, 2,000, 4,000 and 8,000 units per kilo were cured. (6) The therapeutic value of penicillin fractions F, G, and X was compared, one injection every 4 hours for 4 days showed that fraction G was far more effective than fractions F or X.

[These results indicate that the penicillin fraction, the dose, the intervals at which the drug is given, and the duration of treatment, must all be carefully considered.]

T Anwyl-Davies

**Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil.** THOMAS, E W, LANDY, S and COOPER, C. (1947) *J Vener Dis Inform*, 28, 19

The results are recorded of the treatment with penicillin in beeswax and oil of 702 patients suffering from primary and secondary syphilis and of 100 who had relapsed or been reinfected after previous therapy for early syphilis. All received 4,800,000 units in a period of 8 days: one group were given two intramuscular injections about 8 hours apart of 300,000 units daily, the second group had one injection of 600,000 units daily. After 6 months observation, comparison failed to show any advantage in giving two treatments a day instead of one, and subsequently all patients were given a single daily dose of 600,000 units for 8 days.

No serious reactions occurred. 9.6% had low-grade fever about the fifth to the seventh day, 5.1% had pain and induration at the site of injection, and

1.1% had urticaria accompanied by low grade pruritus. Several of the patients with urticaria developed angioneurotic oedema, which subsided within 5 days. In only two cases were injections stopped before the end of the course on account of severe urticaria after 7 days treatment.

Owing to the insufficient time that has elapsed the serological data in the tables must be taken conservatively, for the percentages of failures may become higher with a longer period of observation. The percentages of relapses or re-infections in the serum positive primary cases and in those with secondary syphilis is practically identical for the same period of observation (12.6% compared with 11.0%). Most of these occurred during the first 6 months after treatment. In the series with secondary syphilis 46 cases or 10.5% of those who were examined by lumbar puncture (439) had abnormal cerebrospinal fluid. Of these 46, 26 had a normal spinal fluid 3 to 6 months after treatment. In those cases followed up for at least 6 months, except in secondary syphilis (where the percentage of relapse is 15.2 with single daily injections against 13.2 with two injections daily) the difference in results after the two schedules is not statistically different.

T Anwyl-Davies

**Treatment of Early Syphilis with Penicillin.** STERNBERG, T H. and LEIFER, W. (1947) *J Amer med Ass*, 133, 1

The results of treatment with penicillin of 1,400 soldiers suffering from early syphilis are reported: the total dosage was 2,400,000 units given as 60, 3 hourly injections over 7½ days, 600 (42.8%) of the patients were in the sero-negative primary stage, 564 (30.4%) in the sero-positive primary and 236 (16.9%) in the secondary, about 84% were followed for more than 9 months. Of the sero-negative primary patients 566 showed a satisfactory outcome and 34 unsatisfactory, including 27 infectious and 7 serological relapses. 9 of the infectious relapses may well have been re-infections. 304 patients had their spinal fluids examined and all were negative. Of the 564 patients with sero-positive primary syphilis, 507 showed a satisfactory outcome and 57 an unsatisfactory one of the latter, 20 had infectious relapse, 14 serological relapse, 22 were serum fast, and 2 had abnormal spinal fluids (1 patient came into two of these categories). Of 236 patients with secondary syphilis 196 had a satisfactory outcome and 40 an unsatisfactory one, including 4 with infectious relapse, 6 with serological relapse, 22 who were serum fast, and 3 with abnormal spinal fluids. The total number of spinal fluids examined was 719 and of these 5 (0.69%) were abnormal. 1 was Group I, 3 Group II and 1 Group III. The percentages of satisfactory results for the three categories were 94.3, 89.9 and 83.0 respectively with an average of 90.6. Most of the relapses occurred between the third and ninth months of observation so that it seems possible that, though there may be further relapses as the observation period is extended, these will be offset by some of the serum fast patients becoming sero-negative. As all the patients were treated before February,

1945, it seems probable that the results reported are likely to be better than those obtained later when penicillin samples contained more of the K factor. The failure rate was three times higher in negro than in white patients, it is possible that this may be explained partly by a greater incidence of re-infection in negroes and partly by the relatively larger number of negroes who had reached the secondary stage before being treated.

[Two speakers in the discussion on this paper were confident that a considerable number of re-infections were included in the "unsatisfactory" cases, and one asserted that it was possible to distinguish between relapse and re-infection by carefully conducted serological studies—that is, by performing a "battery" of tests at weekly and monthly intervals following treatment.]

*T E Osmond*

#### Penicillin in the Treatment of Neurosyphilis IV Cerebrospinal Fluid Changes in Cases of Symptomatic Neurosyphilis REYNOLDS, F W (1947) *Ann intern Med*, 26, 393

Penicillin was given intramuscularly to 149 cases of all types of neurosyphilis in doses of 40,000 to 50,000 units 3-hourly, the total dosage ranging from 2,000,000 to 10,000,000 units. In addition, malarial therapy was given to 38 of the cases.

Only 9% of cases still had signs of activity as judged by cell and protein content of the CSF 6 months after treatment started. In all cases the colloidal gold curve showed permanent improvement though the response was not so prompt or complete. The Wassermann reaction in the CSF was lowered in titre, the effect being produced gradually but being well sustained. In only 10% did the WR fail to respond. The degree and rapidity of improvement in the spinal fluid could not be definitely correlated with the dosage of penicillin, the duration of the symptoms, or the extent of abnormality in the spinal fluid. There was some evidence that the colloidal gold curve and WR were more favourably affected if malarial treatment was given concurrently.

*A M Stewart-Wallace*

#### Early Congenital Syphilis Treatment of Two Hundred and Fifty-two Patients with Penicillin PLATOU, R V, HILL, A J, INGRAHAM, N R, GOODWIN, M S, WILKINSON, E E, HANSEN, A E, and HEYMAN, A (1947) *J Amer med Ass*, 133, 10

The results are reported of treating with penicillin 252 infants (219 negro and 33 white) with early congenital syphilis, 118 were boys and 134 girls. The ages at which treatment was given were as follows: under 3 months, 113; 3 to 6 months, 63; 6 to 12 months, 40 [46 in the text]; and 12 to 24 months, 36. The amount of penicillin employed varied from 770 to 150,000 units per kilo of body weight. Results were much the same in the various age groups, but infants treated in the first 3 months did less well than older ones,

probably as a result of lowered resistance, race and sex did not appear to influence the outcome. Spinal fluids of 171 infants were examined before treatment, 22.2% showed Grade I fluids, 29.2% Grade II, and 11.1% Grade III, only 37.4% were normal. It was noted that the older the child the milder the changes in the fluid and the less likely the fluid to be pathological, showing that time alone tends to reverse positive reactions. Treatment had a good effect on fluids, since 72.5% were positive before and 20.9% positive after-treatment. The general effects of treatment were satisfactory in 74%, unsatisfactory in 9%, and in 18% could not be evaluated, only 2.4% showed clinical relapse, and the longer the period of observation the better the results, both clinical and serological, most sera became negative between the fourth and twelfth months. Reactions were few and mild, and the authors consider that there is no need to start with small doses to avoid side-effects. There were 27 deaths (10.7%), but most of these were attributed to causes other than syphilis. It is concluded that the optimum dosage is 100,000 units per kilo of body weight, that penicillin should be administered every 3 hours over a period of 12 to 15 days, and that it is the best single agent yet employed in the treatment of congenital syphilis.

*T E Osmond*

#### Effect of Penicillin in the Treatment of Infantile Congenital Syphilis Further Observations

PLATOU, R V, HILL, A J, INGRAHAM, N R, GOODWIN, M S, WILKINSON, E E, and HANSEN, A E (1946) *Amer J Dis Child*, 72, 635

A year ago the authors published a preliminary report on the results of penicillin treatment in 69 children under the age of 2 years suffering from congenital syphilis. They have now brought this number up to 191 (168 negro and 23 white children), all of whom had treatment solely with penicillin. The average age at which treatment was started was 5½ months, the youngest was 11 days. The authors point out that throughout that year penicillin had been a changing mixture with varying (and diminishing) amounts of impurity and varying proportions of the G, F, X, and K fractions, this may have significantly altered the therapeutic efficacy. No serious reactions occurred, though some fever was noted in 40%, many of the infants had associated non-syphilitic infections which may well have been responsible for a proportion of these. There were only eight reactions apart from fever, all transient and none severe enough to interrupt or modify the course of treatment. When distilled water was used to dissolve the sodium penicillin the injections consistently caused less pain than when normal saline was used.

The results were "little short of dramatic." Dark-ground illumination was always negative after 24 hours of treatment, cutaneous and mucosal lesions resolved within 3 days, and rapid gain in weight in malnourished infants was frequently observed. Rhinitis took from 3 to 6 weeks to heal. Healing of bony lesions was demonstrated in skiagrams in from 3 to 5 months. The general

impression was that recovery was more rapid with penicillin than with arsenic and bismuth therapy. In the cases followed for 18 months or more the Wassermann reaction became negative in over 92% and relapse to a positive reaction occurred only six times. Satisfactory results were obtained in 90% of cases when 40,000 units or more per kilo of body weight were given divided into 120 equal intramuscular injections at 3 hourly intervals. The authors finally recommend a total dosage of 100,000 units per kilo. Eleven cases received more than one course of treatment. There were 24 deaths (12.58%) and though other adequate causes of death were found, syphilis must be considered as contributory in all. Clinical evidence showed that the syphilis had improved or disappeared in 18 of these and the serological titre had decreased or the reaction become negative in 13. The cerebrospinal fluid was examined in 64 cases, was found to be normal in 17, and showed marked improvement after treatment in 31 of the remaining 47. The final evaluation of the efficacy of penicillin in treating congenital syphilis must await the results of trials with other methods of dosage and administration and a clarification of the relative spirochaetocidal and spirochaetostatic effects of the different fractions present in penicillin.

*W F Gaisford*

**Arsenical Encephalopathy An Unusual Case occurring in the Treatment of Congenital Syphilis**  
HIPPS, G and GOLDBERG, R (1947) *Brit med J*, 1, 296

A case of arsenical encephalopathy occurring in a 20-year-old serum-positive congenital syphilitic suffering from interstitial keratitis and iridocyclitis is comprehensively described. There is no record of a preliminary cerebrospinal fluid examination. Systemic treatment had been begun with 17 million units of penicillin 3 hourly and followed by 0.3 g of neoarsphenamine twice weekly for 5 weeks. After an interval of 56 days a similar second course was begun and the first toxic symptoms were manifest 1 day after the fifth injection. Malaise and frontal headache for 24 hours were followed by epileptiform convulsions heralded by an aura of spots before the eyes and accompanied by a cry, tongue biting, and incontinence of urine and faeces, consciousness being regained after 30 minutes. Six of these occurred on the second night after which the patient became comatose, with absent tendon reflexes, bilateral extensor plantar response and conjugate deviation of the eyes to the right. The cerebrospinal fluid was not under pressure and showed the usual raised protein content (170 mg per 100 ml.) and a 012355544 Lange curve with otherwise normal findings.

The treatment adopted included nursing in the erect position, adrenaline, 1 pint of 20% glucose by intravenous drip and 6-hourly injections of calcium thiosulphate, calcium gluconate, and vitamin C. BAL was apparently not used. Coma deepened and the temperature rose to 104° F and later to 105° F at which level it remained until

death 5 days from the onset. Post mortem examination revealed cerebral congestion, pleural petechial haemorrhages, and bronchopneumonia.

*R R Willcox*

**Is Specific Treatment always Necessary in Pregnant Syphilitic Women?** (Er spesifikk behandling alltid nødvendig hos svangre med lues antea?)  
MADSEN A (1946) *Tidsskr norske Lægeforen* 66, 772.

The author discusses the treatment of pregnant syphilitic women who have had previous adequate treatment and who show no obvious signs of disease. His practice is to give a course of treatment in the middle of pregnancy, consisting of 16 injections of neoarsphenamine (0.45 g) and 16 injections of wismol (1 ml) at intervals of 5 to 7 days. In his experience the child always escapes infection with this treatment. In a review of 70 cases of congenital syphilis seen over the last 8 years it was found that only 9 of the mothers had had antisyphilitic treatment before birth. Short histories are given, showing treatment to have been inadequate in 8 cases. The remaining woman had adequate treatment and gave birth to 2 normal children followed by 1 syphilitic infant 4 years later. Evidently treatment before pregnancy does not prevent infection of the child, and a prophylactic course during pregnancy is essential.

*D J Bauer*

## SYPHILIS (PATHOLOGY)

**Preservatives for Syphilitic Serum with Special Reference to the Use of Merthiolate.** CROFT C C and SMITH L L (1946) *J Lab clin Med* 31, 1101

When serological tests for syphilis are required it is preferable to send whole blood to the laboratory. Delay in transit may result in gross haemolysis and decomposition. Under these conditions it is best for the sender to separate the serum himself and dispatch this to the laboratory, unfortunately however it is then common to receive specimens which are unsuitable for testing because of contamination. The authors have therefore investigated a number of antiseptics for their ability to preserve sera without affecting the results of serological tests. Nineteen preservatives were tested in suitable dilutions. Merthiolate gave the best results, sulphomerthiolate was almost equally effective. Phenylmercuric borate and nitrate (1 in 5,000) sulphanilamide (5 mg per ml) and toluol (0.06 ml per 5 ml) did not consistently prevent contamination and 8-hydroxyquinoline sulphate (1 in 2,000) produced a precipitate in the serum.

A concentration of 1 in 2,500 merthiolate was recommended, as 1 in 1,000 more often caused a reduction in titre.

*D G ff Edward*

**Serology in Senegalese in Relation to Syphilis**  
(Serologie syphilitique des Senegalais) JULLIARD  
(1946) *Presse med* 54, 524

Serological tests were performed in French Morocco on batches of 100 patients taken from the native garrison troops, the native local population, Europeans resident in the area, and young Senegalese from the West Coast of Africa. In 17% of young recruits newly arrived from Senegal, in all of whom there was no previous history of venereal disease, there was a strongly positive serological reaction, in 10% it was partially positive, in 12% there was only a partially positive Kahn test, while 61% gave negative reactions. Similar results were obtained with the soldiers who had been more than a year with the garrison. Of 100 Europeans taken at random, only 2 showed partially positive reactions, but 1 of these had a history of a chancre a year before. The other 98 were normal, apart from 10 in whom the Kahn-presumptive test was positive when the standard Kahn was normal. Of the native population of North Morocco giving no previous history of venereal disease, only 4.35% had positive, and 7.6% partially positive serum reactions. Those with a history suggestive of previous venereal disease gave 12.5% positive and 25% partially positive results.

The serological reactions of 3,307 patients attending the venereal disease clinics was compared with those receiving serological tests in general hospitals. In the clinics, Europeans showed 12% positive, 27% partially positive, and 61% negative reactions, the North Africans gave 35% positive, 37% partially positive and 28% negative, while the Senegalese showed 33% positive, 43% partially positive, and 24% negative reactions. In the general hospitals the Europeans showed 6% positive, 17% partially positive, and 77% negative results, the North Africans had 14% positive, 31% partially positive, and 55% negative, but the Senegalese showed 27% positive, 39% partially positive, and only 34% negative.

The Senegalese possessing a positive serology yet giving no history of venereal infection were admitted to hospital and subjected to clinical, cerebrospinal fluid, and radiological examination to exclude the existence of clinical syphilis or yaws. When anti-syphilitic treatment was instituted, it was noticed that where there was evidence of syphilis the serology improved promptly, and in only the exceptional case was the blood still positive after a year, but, where there was no evidence of past or present lues, then little improvement was to be expected in the serological findings. Thus there appeared to be some difference between those cases with positive bloods without signs and those known to be due to syphilis. Simple biochemical tests such as the albumin-globulin ratio did not reveal such distinction, while attempts to transfer the disease by infecting gland material from the first group into rabbits were unsuccessful.

Though many sera from patients suffering from relapsing fever, trypanosomiasis, and malaria were examined, both during and after an attack of fever, the author considers that these diseases were not responsible for the abnormal positive reactions

neither were the intestinal parasites which abound in the Senegalese negro. The fact remains, however, that some 17% of Senegalese have markedly positive serological reactions, and nothing has been found to justify the belief that syphilis is responsible, though there is also nothing to prove that it is not. These anomalies either indicate a different protein constitution in the negro or an allergic state to a disease the aetiology of which is obscure. On practical grounds these cases should not be treated on the basis of serology alone, though perhaps it would be wise not to use them as blood donors.

R R Willcox

**Electrophoretic Analysis of Syphilitic, Biologic False Positive, and Normal Human Sera** COOPER, G R, CRAIG, H W, and BEARD, J W (1946) *Amer J Syph*, 30, 555

The need to devise methods for the differentiation of true syphilitic sera from false positive sera has demanded systematic investigation, including physicochemical examination of the sera. The work here reported is the result of attempts to seek possible characterizing differences of electrophoretic nature between syphilitic and false positive sera. Analyses were made of the distribution, concentration, and mobilities of the serum components characterized by electrophoresis from 28 individuals with a positive serum and known to have syphilis, 32 with a positive serum but with no other evidence of syphilis, and 13 with a normal serum. No qualitative abnormalities peculiar to syphilitic sera were seen, nor was a basis found either for the diagnosis of syphilis by means of electrophoretic analysis or for a differentiation between syphilitic and false positive sera.

V E Lloyd

**False Positive Kahn Reactions Loss of Titer on Storage of Serum in Ice Box** LUBITZ, J M (1946) *Amer J Clin Path*, 16, 768

It had been noted that sera from patients after smallpox vaccination which gave false positive Kahn reactions tended to become negative when exposed to ordinary room temperatures for several days. The author tested the sera of 59 syphilitic patients (92 sera and 219 tests) over a period of 2 to 6 months with the quantitative Kahn test, the sera were stored at  $+2^{\circ}$  to  $+4^{\circ}$  C. Of the 92 sera, 25 (27.1%) showed a moderate loss of titre, 10 (10.9%) showed a gain, and 57 (62.0%) maintained a constant titre. He also tested two groups of false positive sera. Group I consisted of 13 patients with smallpox, 15 with malaria, 5 with upper respiratory infections, 2 with scarlet fever, and 1 each with tuberculosis of bone, infectious mononucleosis, gonococcal, arthritis, lymphogranuloma venereum, and a "general biologic reaction", 109 sera were taken and 208 tests carried out, all showed a decrease of titre or became negative at various periods, usually within a month. Group

It consisted of 1 patient with pinta whose serum maintained its titre for 3 months, and 5 with leprosy 2 sera maintained and 4 lost titre. Illustrative cases with results of serum tests are given in seven tables. That the serum from the patient with pinta maintained its titre is not considered surprising, since the disease is due to a spirochete, the reactions of the leper sera are not so easily explained. The loss of titre in general may be due to non-specific antibody being more labile, or to an inhibitor, present in the serum, becoming activated, the difference in behaviour of syphilitic and non-syphilitic sera suggests that the two types of antibody are not the same.

T E Osmond

**Agranulocytosis** Report of Twelve Cases in which it followed Intensive Arsenotherapy for Syphilis FISHER, S HOLLEY, H L., and FEIN, G (1947) *Arch Derm Syph., Chicago*, 55, 57

This report deals with 12 cases of severe agranulocytosis whose total white-cell-counts ranged between 1,000 and 4,800 per c mm, at some stage 6 showed a complete absence of granulocytes, and the remainder polymorphonuclear neutrophil percentages of below 14. Eight of these cases developed among 504 patients treated on a 25-day schedule consisting of single injections of not more than 60 mg. of mapharsen given 6 days a week for 22 days and combined with 200 mg of bismuth subsalicylate every 5 days. In 16 cases the arsenic was discontinued because of toxicity. Two occurred in 483 patients treated by injections of mapharsen given daily for 20 days and combined with bismuth as before. In 28 treatment was modified because of toxic reactions. One arose among 895 patients treated with 8 daily injections of mapharsen, 3 injections of bismuth, and multiple injections of penicillin to a total of 600,000 units in the same time. Toxicity led to discontinuation of treatment in 14. In all, routine blood counts were performed every 5 days, and in those affected had been normal in the first instance. One additional case is described as occurring in a patient with secondary syphilis after only 4 weekly injections of neoarsphenamine.

All 12 patients were negroes between 17 and 39 years. Ten were females, 2 of whom were pregnant. Six suffered from early latent syphilis the remainder from early syphilis. Six had received previous arsenical treatment, and 2 had recently had sulphonamides also. Six had warning febrile reactions (2 with ninth-day erythema) and in 2 others the treatment was temporarily suspended on account of headache or nausea. In these 6 cases agranulocytosis supervened after resumption of the mapharsen. The complication generally occurred near the end of the course and was usually associated with malaise, headache, sore throat, and a temperature ranging between 101° and 105° F (38.3° to 40.6° C) which lasted 5 to 14 days. The blood counts returned to normal when the fever had subsided.

Treatment was by means of intramuscular pent-nucleotide (10 ml 6-hourly), daily injections of liver extract, and BAL (12 ml. over 48 hours

followed by 12 ml over 6 days). Three patients had multiple transfusions, and intravenous 5% dextrose and mouth washes were also given. No deaths occurred, and eventually all patients fully recovered.

R R Willcox

**Secondary Syphilis, Sickling, Malaria, Sulphonamide and Herxheimer Reactions in an African Soldier** WILLCOX R. R (1947) *Brit J Derm Syph* 59, 59

A case of secondary syphilis in an African is described in whom skin lesions and an acute sickling crisis occurred after the administration of sulphonamide and mapharside. The author suggests that the Herxheimer reaction and sulphonamides may have precipitated the sickle-cell crisis, or alternatively that the reaction was induced as the result of a sickling crisis.

R Winston Evans

**Palpable Epitrochlear Glands Incidence and Relation to Syphilis** MARTIN, L (1947) *Lancet* 1, 363

Systematic palpation of the epitrochlear lymph nodes in a series of 200 soldiers in none of whom any affection which might have led to their enlargement had been detected, showed that 42% had palpable nodes which in 17 cases exceeded the size of a cherry stone, and in 33 cases were unilateral. Comparable results were obtained in a series of 100 civilian males and no significant difference was found between manual and non-manual workers. It is concluded that the statement that such enlargement is particularly associated with syphilis has little evidence to support it.

S S B Gilder

**Visual Field Changes in Syphilis of the Central Nervous System** MCLEAN J A (1946) *Canad med Ass J* 55, 571

The pathogenesis of syphilitic primary optic atrophy as discussed in recent American publications is reviewed. Its association with tabes dorsalis and tabo-paresis and the rarity with which it occurs in general paresis suggest a common pathogenesis with tabes dorsalis. Deficiency of vitamins A and B may operate in addition to the neuro-syphilitic process. One view is that there is actual primary degeneration of the optic nerve fibres while another states that the optic atrophy is secondary to involvement of the nerve in a chronic inflammatory process sometimes associated with syphilitic basilar meningitis. There is general agreement as to the value of visual field estimations both in early diagnosis and in measuring the progress of the condition or its response to treatment. The field changes vary from case to case, but the field defects in each eye of a particular patient show a marked similarity. In colour fields, red and green fade first, blue and yellow later, and white last. In treatment, the trivalent organic arsenical and bismuth preparations are of little, if any, value. Tryparsamide is nearly always contraindicated, but success from its cautious use is claimed in a very small proportion



58.8 for the special, 39.6 for the Peizer, 37.9 for the "difco," and 10.2 for the Mueller medium

R R Willcox

**Observation on the Direct Oxidase Test as Applied to Gonococcal Colonies Grown in Certain Media** BUCCA, M A, THAYER, J D, and SCHUBERT, J H (1947) *J. Ven. Dis. Inform.*, 28, 40

In experimental work with different culture media for the gonococcus, the rate at which the oxidase test became positive was found to vary. This inconsistency was more marked in the meat-free chocolate cystine blood-agar described by Huffer and Hill, and hence this medium was varied and compared with a modified McLeod horse plasma and hæmoglobin medium [See above abstract]

The oxidase reagents used were a 1% aqueous solution of dimethyl-*p*-phenylenediamine monohydrochloride and a preparation of the same substance adjusted with a 3.45% admixture of a 10% solution of sodium carbonate to a final pH of 6.92. A naphthol-diamine reagent, which consisted of a 1% aqueous solution of the diamine reagent as before, with 0.144%  $\sigma$ -naphthol in 50% ethanol and 0.044% sodium carbonate, with a final pH of 5.52, was also employed. Of 107 gonococcal cultures on the Huffer-Hill medium, 48.6% gave atypical oxidase reactions with unadjusted diamine reagent, and 4.7% no colour reactions. With the naphthol-diamine reagent, only one plate (0.9%) showed an atypical reaction. With modified McLeod medium 100% of cultures gave typical oxidase reactions with both oxidase reagents.

A larger number of atypical reactions were observed when 1% glucose was added to the medium irrespective of the presence of horse serum or chocolate human blood. When buffer salts were added to such media containing glucose, normal oxidase reactions were seen with both adjusted and non-adjusted diamine reagents. When 1% pyruvic acid, an intermediate product of glucose oxidation, was added to such media containing glucose, there was no effect on the oxidase reactions, though if phenol red was used as an indicator it could be shown that abnormal reactions would occur with both acid and alkaline reacting colonies.

R R Willcox

## OTHER VENEREAL DISEASE CONDITIONS

**Streptomycin Treatment of Urinary Tract Infections With Special Reference to the Use of Alkali** HARRIS, H W, MURRAY, R, PAINE, T F, KILHAM, L, and FINLAND, M (1947) *Amer. J. Med.*, 2, 229

There have been reports in the literature of a high percentage of failures in treating urinary tract infections with streptomycin in spite of the fact that *in vitro* sensitivity had been proven. It had previously been suggested that during treatment it was important to maintain alkalinity

of the urine. In this series 7 cases were treated with streptomycin alone and 7 in conjunction with alkalis. The results are indicated in tables, one of which is reproduced below.

**Results of Streptomycin Therapy in Relation to Adjuvant Alkalis and the Appearance of Resistant Strains**

Results of treatment	Total cases	Alkaline urine	Acid urine	Developed resistance
Cured	9	8	1	1*
Transient improvement †	6	6†	0	1
Failure	3	0	6	6

\* Patient received alkali. Resistant strain isolated only once after treatment and subsequent cultures were negative.  
† One of these patients was free of infections for over 5 weeks and was considered as having a reinfection, since a different organism was found later.

[Readers are referred to the original paper for full clinical and bacteriological details.]

W G Gill

**So-called Triple-symptom Complex of Behcet** THOMAS, E W P (1947) *Brit. med. J.*, 1, 14

In 1937 Behcet described a syndrome in which eye lesions (ranging from conjunctivitis and corneal ulceration to hypopyon uveitis) occur in association with ulcers of the mouth and external genitals. The ulcers of the mouth and genitals are small and discrete. Other skin lesions, such as erythema nodosum or an acneiform eruption, may also occur. The disease affects men twice as often as women, occurs predominantly in the third decade of life, and runs a relapsing course over a number of years. It is believed to be due to a filterable virus. A similar combination of symptoms had been reported by Whitwell in 1934 and by Nishimura in 1935, since 1937 a number of other cases has been published. A case recorded by Berlin in 1944 is of interest because the central nervous system was involved. The patient eventually developed headache, giddiness, and fits, which culminated in coma and death. At necropsy small multiple foci of inflammation and softening were found in the brain. The subject has been reviewed by Curth, who described the first American case of the disease. There was no response to systemic penicillin or to the sulphonamides. Three cases were also reported in male Arabs. The ulcers were accompanied by hypopyon iritis and hæmorrhages in the retina and vitreous, in 2 there was also relapsing epididymitis.

In the first case to be reported in this country, the patient, a married man aged 29, had suffered intermittently since the age of 21 from ulcers of the tongue, roof of the mouth, and inside of the cheeks. In June, 1940, he developed relapsing iritis of the right eye, and subsequently thromboses

of the right femoral vein and the inferior vena cava. The left eye then became involved. A detailed search, including examination of the cerebrospinal fluid, radiographs of the skull, and an encephalogram, failed to reveal any focus of infection. Shortly afterwards skin lesions of three types appeared: (a) small, slightly tender papules on different parts of the body, particularly the forehead, cheeks, and legs; (b) small patches of erythema, thought to be due to thrombosis of a surface vein; (c) larger, more tender nodules like those of erythema nodosum, particularly on the thighs. Intense pain developed in the right eye, which was excised. Later vision failed completely in the left eye, which was also enucleated. The ocular condition is described as a subacute iritis with hypopyon with, later, choroidal lesions and glaucoma. Histological examination of the excised eyes threw little light on the aetiology. There was complete detachment of the retina with gross intraocular hæmorrhage, chiefly subretinal, and marked patchy thickenings of the ciliary body and choroid, with reactionary changes but there was no certain evidence that vascular thrombosis was the initial factor.

Geoffrey McComas

#### Universal Serologic Reactivity with Lipid Antigens Basis for False Positives. KAHN R. L. (1947) *Amer J publ Hlth*, 37, 283

Lipid antigens which are highly specific for syphilis may be so employed as to give nearly 100% of positive reactions in non-syphilitic persons. These 'universal reactions' are best shown in variations of precipitation technique, but can also be elicited with complement fixation tests.

By employing 10 negative and presumably non-syphilitic sera, deviating from the standard Kahn technique by using 0.3% instead of 0.9% sodium chloride as a diluent, and reading the tests after 24-hours incubation in an icebox instead of immediately, the author obtained nine positive results. The tenth serum became positive when a sensitized antigen was employed. When cardiolipin and Kahn antigens were used at 1°C without shaking all sera showed some precipitation, which disappeared on agitation. By omitting the diluent and employing Kolmer antigen, the author obtained some precipitation in all 10 sera. A characteristic of these 'universal reactions' was that the precipitates could be dispersed by strong sodium-chloride concentrations: as little as 0.1 ml. of 5% solution removed them in a few minutes.

These reactions favoured by cold and low chloride concentration are thus induced under conditions similar to those employed in the Kahn verification test as an aid in the detection of false-positive reactions. The behaviour of serum which had given a false positive reaction was therefore studied and contrasted with that of sera shown to be negative and positive to the standard technique, all of which also showed 'universal reactions'. The sera were serially diluted with water and with sodium-chloride concentrations of from 0.3 to 0.9%, mixed with Kahn antigen

suspension in the ratio of 6:1 shaken for 3 minutes, and diluted with the same sodium-chloride concentrations as had been used in making the serial dilutions of the serum. The results were then read without incubation of the mixtures and after 4 and 24 hours incubation in the icebox. The universal reactions were most evident after incubation, while without it the false-positive serum showed the most marked reactions when serially diluted with water and least reactivity when diluted with 0.9% saline. The negative serum did not show the tendency to reach the 0.9% saline level, but the positive serum reacted most in this tube and very little in the water column. After incubation of the mixtures at low temperatures 'universal reactions' only were seen. It is therefore suggested that false-positive reactions are really highly potent 'universal reactions' which have passed the serodiagnostic threshold.

R. R. Wilcox

#### Observations upon the Specificity of the Complement Fixation Test for Lymphogranuloma Venereum. DULANEY A. D. and PACKER, H. (1947) *J Immunol* 55, 53

Complement-fixation tests were carried out on sera from five groups of individuals with a specific lymphogranuloma antigen of chick-embryo origin (lygranum) and a control antigen of normal chick-embryo material. Tests were also made with a Wassermann antigen. Group 1 comprised 148 medical students with no clinical evidence of venereal disease. 138 were unselected and 10 were selected because of upper respiratory infections (in view of the antigenic affinity of some of the pneumonia viruses with the virus of lymphogranuloma). Group 2 included 42 children (5 white, 37 negro) all of whom had had a febrile illness. Group 3 comprised 22 negro children with congenital syphilis: all were below the age when acquired venereal infection might be expected. Group 4 contained 81 patients (53 white, 28 negro) with neurosyphilis who had been infected at least 2 years previously. In Group 5 there were 214 patients with infective ano-genital lesions. In all tests the initial serum dilution was 1 in 5.

Group 1.—Of the 148 sera from this group all gave a negative Wassermann reaction, while 13 gave positive reactions with the lygranum antigen—12 in the unselected group, 1 in the respiratory infection group. Of these 13 positive sera 10 showed titres of 1 in 5 or 1 in 10 while 3 were positive in dilutions of 1 in 20. None was positive in higher dilution. None gave a positive reaction with the control antigen. Group 2.—One serum with a negative Wassermann reaction gave a positive reaction with the lygranum antigen. Titre was low (1 in 10), and the authors considered the reaction a non-specific one. Group 3.—No positive reactions were obtained with the lygranum antigen, a finding which casts doubt on the view that late syphilis is a frequent cause of non-specific reaction in this test. Group 4.—White patients gave 43% positive reactions with lygranum antigen, negro patients 82% positive. As the Wassermann reaction was positive in all

cases, it appears that factors other than cross-reactivity with syphilis are responsible for the high proportion of positive lygranum tests in the negro group. Group 5—Of the Wassermann-positive sera in this group 83% gave positive reactions with the lygranum antigen, as compared with 68% of positive reactions among the negative sera. Results in Groups 4 and 5 show, therefore, no significant difference in the incidence of positive lygranum complement-fixation reactions in the Wassermann-positive and Wassermann-negative individuals. However, the high overall incidence of positive lygranum reactions in those individuals with proven or suspected syphilis prompted the authors to carry out titration studies on 142 positive sera from Group 5, with serum dilutions higher than 1 in 5. At these, 56% gave titres of 1 in 40 or above, but of 33 sera from patients with a clinical diagnosis of lymphogranuloma venereum 97% showed titres of 1 in 40 or above.

From these and other data obtained in this survey the authors conclude that if the 1 in 5 serum dilution is alone used, non-specific reactions may be expected, when the sera are titrated in dilutions of 1 in 20 and 1 in 40 the test is of value in diagnosis. A titre of 1 in 40 or above affords good evidence of specific infection, with a titre below this quantitative examination of subsequent specimens of sera is advisable. False-positive reactions can usually be eliminated by titration studies in which the 1 in 40 dilution is considered as critical or by absorption of sera with Kahn antigen.

T D M Martin

**Effect of para-Aminobenzoic Acid on Lesions due to Ducrey's Bacillus** (Azione dell'acido para-aminobenzoico su lesioni provocate dallo streptobacillo del Ducrey) CALETTI, G (1946) *G Ital Derm Sif*, 87, 485

After a short review of recent papers dealing with the antagonism—*in vivo* and *in vitro*—between para-aminobenzoic acid and the sulphonamides, the author reports his clinical experiments in 9 cases of ulcer produced by Ducrey's bacillus, where treatment with a specific vaccine was given together with local application of a para-aminobenzoic acid ointment.

Some ulcers were of venereal origin and some were experimental, produced by material taken from venereal ulcers inoculated into healthy human skin. The author confirms his previous observations that this type of ulcer can be cured with three to four intravenous injections of a specific vaccine—"ducreina"—given in increasing doses ( $\frac{1}{2}$ ,  $\frac{3}{4}$ , and 1 ampoule) at intervals of 3 days. If, however, an ointment of para-aminobenzoic acid (10%) was applied for 7 to 8 days before and also during the vaccine treatment, not only did no improvement

take place but considerable enlargement and deepening of the ulcers were observed. Even an increase in the number of injections did not alter the unfavourable results. In all cases it was found necessary to discontinue the application of the ointment for a cure to be achieved.

A particularly interesting experiment is described by the author. Material taken from a chancroid on the prepuce was inoculated into the right and left thighs of the same individual, and after a few days an ulcer developed in both these areas. Para-aminobenzoic acid ointment was now applied twice daily to the ulcer on the left thigh only, and injection treatment was started after a week. After four intravenous injections with the specific vaccine it was noticed that the ulcers on the prepuce and the right thigh, which were not dressed locally, had completely disappeared, while the ulcer on the left thigh had become larger and Ducrey's bacillus was still present. These observations lead the author to speculate on the cause of the antagonistic mechanism, and he tries to find a satisfactory interpretation of this interesting phenomenon.

E. Kost

**Streptomycin in Experimental Chancroid** MOR-TARA, F, and SAITO, M T (1947) *Amer J Syph*, 31, 20

These authors, who have already found *Hæmophilus ducreyi* to be remarkably sensitive to streptomycin hydrochloride *in vitro*, record the results of treating 11 rabbits, previously inoculated with living cultures of the organism, with this antibiotic. The disease in rabbits is self-limiting, taking the form of a small abscess from which the organism can be recovered in pure culture. The lesion heals spontaneously within 6 to 8 days.

Development of lesions was prevented in 7 rabbits to which 150,000 units of streptomycin had been given in three equal doses within 24 hours, treatment being started from 1 hour before up to 4 hours after inoculation. Smaller doses of 25,000 units 1 hour before and 2 and 5 hours after inoculation appeared to protect 1 animal, though 50,000 units 1 hour before and 3 and 24 hours after modified but did not prevent the development of the disease in a second animal. Two other rabbits had 25,000 and 50,000 units respectively 7½ hours after inoculation. The resulting lesion appeared to be modified by the larger dose, but the effect on the smaller one was minimal. Eleven inoculated rabbits served as controls. All developed pustules approximately 10 mm in diameter within 48 hours. The authors suggest that clinical trials of streptomycin in chancroid are warranted, and that the treatment might be particularly useful in sulphonamide-sensitive patients.

G L M McElligott

# THE CONTROL OF VENEREAL DISEASES UNDER THE NATIONAL HEALTH SERVICE\*

BY

L W HARRISON

*Late Adviser in Venereal Diseases to the Ministry of Health*

The present time seems appropriate for a discussion on the control of venereal diseases under the National Health Service because important discussions on working arrangements, terms, and other matters are now taking place between representatives of the medical profession and the Ministry of Health, and large numbers of medical practitioners who have served as specialists in the Armed Forces are wondering whether any and what use is likely to be made of their skill and experience when the new Service is set up

It seems natural to enquire whether the National Health Service is likely to provide conditions for the control of venereal disease that are an improvement on the present, and if so in what respects, also whether it is likely to provide employment for more specialists in venereal disease than under present conditions. Without prejudice to any views I may hold on the National Health Service generally, and speaking only for the Service as it concerns England and Wales I think that a wonderful opportunity is offered for improving the present venereal disease service. In support of this, I would first offer some criticisms of the venereal disease service under present conditions

## The Present Position

At present the authorities responsible to the Minister of Health for arrangements under the Public Health (Venereal Diseases) Regulations, 1916, are the County Councils and the County Borough Councils, who are required to provide facilities for the examination and any necessary treatment of persons suspected of suffering from syphilis, gonorrhœa, and/or soft chancre and for the laboratory examination of specimens of material from such

persons. They are also required to work Regulation 33B as long as it is in force, and they are exhorted by the Minister of Health to educate the public in the facts about venereal diseases, to provide social service designed to encourage attendances for treatment to follow up those who discontinue attendance prematurely, and to trace and persuade contacts to undergo examination etc.

In all this work they are allowed, under the Local Government Act of 1929, a large amount of discretion. Provided that medical officers appointed to charge of treatment centres comply with certain requirements in respect of knowledge and experience—requirements which were designedly made very mild in 1930 when specialists were relatively scarce and posts in country centres were not easy to fill—they need not submit any appointment for approval by the Minister of Health, this is unlike the position before 1930 when the Minister could always ask an appointing authority to choose again. The appointment now may be made by the governing body of a hospital or directly by a local authority according to the locus of the treatment centre, but there is no provision to ensure that the electing body is qualified by knowledge of the requirements to choose the most suitable candidate. In such circumstances it is perhaps not surprising that on occasion the most suitable candidate has not been elected.

The approval of the Minister of Health is not necessary for any change in the arrangements that does not involve a curtailment of facilities. On the other hand, except in the case of expansions necessitated by war conditions and recognized as such by the Minister, the local authority cannot look to the Minister for reimbursement of any part of the cost of any improvement which they may make in

\*An address to the Medical Society for the Study of Venereal Diseases July 26 1947

their venereal disease service until the end of the five-year period when the amount of their block grant for all grant-aided services is re-fixed, as during the years 1916-30 local authorities were educated to expect reimbursement of 75 per cent of their expenditure on venereal disease, the present conditions of repayment are discouraging. If a centre has become too small for its turnover, if there is shortage of staff, if the number of sessions per week has become too few for the work to be properly done, if the hours spent by the medical staff over the work have become more than were calculated necessary when the salaries were originally fixed, if in fact the staff is being sweated, then the remedy depends on a body which probably starts to consider the matter with a strong bias against incurring more expenditure and, being ignorant of the requirements, does not feel the urgency of the matter. In such circumstances it may not be surprising that, on occasion, delaying tactics are employed. The question is referred to a committee, which instructs the medical officer of health to make a report. In due course the report is presented, but then perhaps it is too close to the municipal elections for the matter to be considered by the Council and it is postponed until after the elections. Meantime the medical officer of the treatment centre struggles on, unhappily seeing his centre become what Surgeon-General Parran has so aptly described as a treatment mill.

#### TREATMENT CENTRES

Treatment centres under present conditions are more or less self-contained units, and in many cases the medical staff consists of only one medical officer. In the Provinces particularly, the frequent result of this is that when such a medical officer cannot attend his place has to be filled temporarily by someone, such as a resident medical officer, who may be very inexperienced in the management of venereal disease. Moreover, the treatment centre is often in a place where there is not enough venereal disease to employ a medical officer whole-time, and the medical officer of the treatment centre is not only primarily interested in some other branch of medicine but in respect of venereal disease he "ploughs the lonely furrow," having nobody near him with whom he can talk shop. A census which I made in 1939 of the medical staffs of the 156

centres in the Provinces in England, showed that they had 259 medical officers (216 male and 43 female), and, of the 259, only 36 were primarily specialists in venereal diseases. Of the remainder, 16 were described as dermatologists, 14 as pathologists, and 66 as medical officers of health or assistant medical officers of health. I need not detail the prime interests of the remainder. Even in London, where there were 23 centres with 98 medical officers, only 11 of the centres had medical officers who were primarily specialists in venereal disease, and there were 10 dermatologists, the remainder were described as physicians, surgeons, pathologists, anaesthetists, general practitioners, electro-therapists, and psychologists.

#### AVAILABLE PERSONNEL

At the present time, as we know, there are a large number of medical practitioners who have gained valuable experience in the management of venereal disease whilst serving with the Armed Forces, but their appointment to charge of or service in venereal disease treatment centres depends on (a) the occurrence of vacancies created by casualties in the existing staffs, and (b) their election by committees which very often do not know the requirements. Further, the conditions of many of the lonely appointments are such as whole-time specialists in venereal disease could not accept because, with due regard to economy of public expenditure, the salaries which can be offered for charge of such small centres cannot be sufficient in themselves for the maintenance of a medical practitioner.

It does not seem necessary here to criticize the section of the venereal disease service which depends on the work of practitioners enrolled under the Ministry of Health's Circular No 2226 to treat patients in their own surgeries because it can be dealt with adequately when we speak of the venereal disease service as one hopes it will be under the National Health Service.

#### THE LABORATORY SERVICE

There remains for criticism the laboratory section of the venereal disease service. In too many laboratories which have been approved under the Venereal Disease Regulations the work of serum-testing is relegated to technicians. The Local Government (Qualifica-

tions of Medical Officers etc) Regulations, 1930, lay down certain fairly stringent conditions for qualification as an approved Venereal Disease Pathologist for the purposes of the Venereal Disease Regulations, and it must be obvious that those conditions were drafted with the intention that only persons possessing them should be entrusted with serum testing and the other work of a venereal disease pathologist. Relegation of this work to a technician who is not qualified under the Regulations is a breach of the Agreement under which the institution which houses the laboratory in question carries out the work under the Venereal Disease Regulations in return for fees calculated on the assumption that a fully trained and experienced pathologist would do it. The common reply to the criticism that the approved pathologist at a given approved laboratory does not actually perform the tests is that although he does not do so, he supervises the work of the technician and holds himself responsible for its accuracy. However, anyone with experience of serum testing knows that one could supervise serum testing adequately only by watching the measurement of every reagent and its addition to the tube that has been laid out for its reception, very little imagination is needed to realize that under such conditions the supervisor might just as well do the work himself.

### The Future

How can the venereal disease service be improved through the operation of the National Health Service? First, I suggest that in each region there should be a regional consultant who is director of a treatment centre in the region. The consultant should be appointed by the Minister of Health, and he should be a member of the Regional Hospital Board, or at least be co-opted by the Board whenever the subject of venereal diseases is discussed. His duties should include (a) assistance to directors of treatment centres in his region in securing conditions conducive to the efficiency of their centres, (b) supervision of the practitioners employed under the provisions of the Ministry's Circular 2226, or its equivalent, to see patients in their own surgeries if this service is considered worth continuance, (c) securing and maintenance of a proper liaison between the treatment centres and the social services under the medical

officers of health in respect of such work as the tracing of contacts by visiting whenever contacts cannot be secured by other means, (d) the organization of regional conferences of venereal disease officers for discussion of matters of interest to the regional venereal disease service.

### THE TREATMENT SERVICE

The treatment service should comprise treatment centres in the towns, and for rural areas a general practitioner service on similar lines to that now operating under the Ministry of Health's Circular No 2226.

The treatment centres should be of two main kinds: headquarters and subsidiary, and every subsidiary centre should be staffed by the headquarters centre to which it is subsidiary. Such an arrangement would have the advantages that (a) every centre would eventually be staffed by specialists in venereal disease, or by practitioners who for the time being were working only in this branch of medicine, (b) there would be no ploughing the lonely furrow by directors of small venereal disease treatment centres, and (c) there would be continuity of skilled service practically undisturbed by casualties to individual members of staffs. The staff and equipment of subsidiary centres might well be transported there in motor vehicles, thus every such centre could have practically as good equipment as that in a headquarters centre, even to an incubator which could be paraffin-heated and fitted into the motor vehicle.

Directors of headquarters centres should be elected by Regional Hospital Boards, helped by the advice of their regional consultants. Assistants in a venereal disease treatment centre should be appointed by the Management Committee or the Board of Governors of the hospital responsible for the general administration of the headquarters centre.

### THE SOCIAL SERVICE

For the social service each centre, whether headquarters or subsidiary, should have one or more almoners, for the encouragement of attendances for following up defaulters, and for persuasion of patients to persuade their contacts to attend. But for such contact-tracing as requires domiciliary visits the social services of public health departments should be employed.

## LABORATORY TESTS

Laboratory tests will presumably be carried out for the most part in the laboratories of the hospitals at which headquarters centres are established. My view is that when the venereal disease service is established under the National Health Service steps should be taken to ensure that laboratory tests of material from persons suspected of suffering from any of the venereal diseases are carried out by officers who possess at least the qualifications laid down for venereal disease pathologists in the Local Government (Qualifications of Medical Officers etc.) Regulations, 1930. Further, I think that the Venereal Disease Reference Laboratory should be continued.

It is far too little realized at present that the testing of a specimen for evidence of venereal disease is a serious matter which may affect the whole future of the person from whom the specimen was derived. Every specialist in venereal disease must often have wished that he could bring home to the responsible pathologist the distressing consequences of a false positive serum reaction. The responsibility for the consequences of a false positive cannot lightly be shifted to the clinician by saying that the pathologist does not make the diagnosis. In certain circumstances the evidence of the pathologist may be crucial. Some months ago I was asked to see a married man, a member of one of the learned professions who for three months had been attending a dermatologist for what I proved to be a syphilitic rash, the proof was by demonstration of *S. pallida* in the juice from a typical mucous patch and by the serum reactions. Everything was open and aboveboard in respect of domestic relations, perhaps chiefly because it was clear that the infection must have been acquired innocently, and at once steps were taken to have the wife's blood tested. The test was done by a laboratory to which the family practitioner sent the specimen, and the report was that the Wassermann reaction was strongly positive. Fortunately, I had advised that, although the chances of the wife being infected seemed very strong, they should on no account accept the first test as conclusive whether the report was positive or negative. In consequence of this I had the

opportunity to take further specimens of blood of which three in succession were found completely negative, one of the specimens being tested in two laboratories. In this case the husband was a highly-strung intellectual who went through hell in the interval between my diagnosis of his own condition and the first negative. I need say no more to emphasize that we ought all to press hard for the principle that the venereal disease pathology must be in the hands of people who have been thoroughly trained in the work and are moreover fully conscious of the implications of their reports.

In my view the Venereal Disease Reference Laboratory is still a necessity. It originated in 1924 from the difficulty of persuading venereal disease pathologists that their respective test methods might be worth revision. It is useless arguing with a pathologist that one would judge from his protocols that his test could be improved, the only thing to do is to invite him to test 200 or more sera supplied to him from a central source, in parallel with a reliable tester practising a method which has itself been through the fiery ordeal of a comparison of methods applied to a large number of unknown sera. On these lines a fairly large number of comparisons were run between 1924 and 1939 and in each case the results of both pathologists' tests were put together side by side with the clinical diagnoses, which were disclosed to the pathologists only after the results had been reported, the effect frequently was some heartburning and often also a determination to revise a test method. Further the Venereal Disease Reference Laboratory has often acted as a court of appeal in the case of anomalous results, and during the late war it was a godsend to many laboratories in providing reagents for serum tests, including preserved complement serum in a liquid state. The Venereal Disease Reference Laboratory has been transferred to the Medical Research Council, and I should like to emphasize that there is no idea in my mind of making the pathologist in charge of it in any way a supervisor of venereal disease laboratories.

The venereal disease service has few friends outside its own ranks, and we shall get efficient conditions only by fighting hard for them.

## DISCUSSION ON THE PRECEDING PAPER

DR. LAIRD trusted that Col Harrison's counsels would bear fruit and that the modern set up would be as close to the proposals he had put forward as possible. There was only one specific point he would like to add: he thought that not only should there be conferences between the venereal disease staff of the region but that there should also be inter regional conferences at least between the directors of each region.

DR. McLACHLAN said that many wondered what would happen when the new scheme came into operation and they departed from public health to hospital service. Some had said: "The only thing which will be different will be the signature on the bottom of the pay cheques." That was a view he did not entirely share.

In venereal disease there were various sets of problems and a solution effective in the compressed urban areas such as London would not always be so in the rural areas. Bristol had a town population of over half a million, but there were also many patients in rural areas. Dr. McLachlan was depressed about the standard of diagnosis and treatment at many outlying clinics and wondered what mechanism a regional director would have to raise the standard. He agreed that regionalization and central recording should make many problems, for example those of contact tracing, much easier. A number of cases of double notification under Regulation 33B had been found recently: for example one in Bristol and the other in an adjacent administrative area. Some of the more refractory patients had only been brought under treatment when the two Forms 1 were finally linked. A regional scheme would make contact tracing easier and more complete.

While all the schemes were primarily directed to treatment, there existed a great need for research into serology, the efficacy of drugs and so on. He felt that venereologists should be encouraged to do some wider research and not necessarily be limited as at present, to the investigations they could carry out along with their routine clinical work.

DR. LETTIA FAIRFIELD spoke not primarily as a venereologist, but as someone interested in the hospital services. When the National Health Service took over next year there would be great difficulty in implementing the public expectations of medical services. The nursing situation was such that it would be difficult to get enough nurses to deal with acute surgery with midwifery and with other urgent and acute hospital problems. When there was competition the venereal disease service was pushed to the bottom of the list. However well disposed the regional authorities might be, and however well organized unless the venereal disease service itself had a very fair idea of what it wanted and why, under the amalgamated service conditions would be even worse than they

were today. It was important to make the demands as economical as possible.

With regard to the question of the efficiency of the present service there was some anxiety about the standard all over England. She would give two examples. When she was appointed in 1940 to look after the medical service of the A.T.S. she found that the A.T.S. had not been allowed a specialist venereal disease service of its own and had to use the existing civilian service for the women. The appalling standard of the work of this service in whole areas caused inexpressible anxiety. It was dreadful to realize that it was the only service available to the civilian population in parts of England and Wales after twenty-five years of venereal disease schemes. When the A.T.S. got its own specialist staff going in the R.A.M.C. and could look into the results of their work and check it up, the kind of result which was wanted for the civilian population was obtained.

The second matter was the question of false positive blood tests. The London County Council was the first big authority which started to do routine Wassermann tests for very large antenatal clinics and it was found that large numbers of false-positive results were reported. Often when the history and after-history had been carefully gone into there was great doubt about the diagnosis of syphilis being correct.

She hoped that there would be a close liaison with the new public health service for social work. There was still a tendency in some clinics at present to ignore the social aspect. The attitude to social service in many of the hospital clinics—particularly in the provinces—was often apathetic and education was needed not only among the general public but amongst their own ranks. She hoped that the regional bodies would co-operate readily with the health staffs for job-finding, contact-tracing, etc.

DR. DOUGLAS CAMPBELL said the regional scheme had had a good preliminary trial under Army auspices where Brigadier Osmond had control of specialists, advisers and consultants serving over large areas. Conferences were held under his chairmanship at the War Office and some of the medical officers were able to come back from regions overseas to partake in these conferences and give opinions from the field. It was to be hoped that such a scheme could be devised to link up venereology all over the country.

Although the Army had provided some very efficient venereologists some excellent trainees and some quite good technicians nevertheless frustration and difficulties were experienced. The work of the venereologist, especially in the difficult times of sulphonamide resistant gonorrhoea and until penicillin was available was a twenty-four hour job and was often done under the worst possible conditions. Almost without exception the average colonel commanding a hospital who found that he had to provide room for a venereal



disease unit was disgusted to the degree that he insulted the persons picked upon. They were disliked because they were venerologists, they got the least help, and the worst provision of accommodation and staff. The work of the special venereal disease treatment orderly was infinitely more important than that of many nursing sisters in that he was left on his own, but the means of selection of the special treatment orderly very often was to parade the worst men in the unit and say, "Go and be taught to be special venereal disease treatment orderlies." He did not think that they would be a great deal better off under the regional body.

Dr Campbell thought that, with few exceptions, the venereal disease department did not get its adequate position in a hospital, certainly not as regarded building and other accommodation. Unless a strong position was taken up by the Society in the immediate future, all the shortcomings of the present scheme would be carried forward, the longer it was left the more difficult it would be to rectify the matter.

It was the opinion of many that venereal disease pathology would be passed to the general laboratory. Col Harrison had raised the question of the very high standard necessary. In the Services they were dependent on a general laboratory to do serology, and very often the pathologist, eminent as he might have been, had never done, much less supervised, venereal disease serology and one spent many difficult hours trying to sort out the conglomeration of results obtained from these otherwise efficient laboratories. He was afraid it was part of the scheme that the maligned venereal disease laboratories would die out and their work become a minor part of the laboratory service.

MR A J KING said that there were arguments against adding to the numbers of specialist diplomas—there were already so many of them, but on the other hand unless there was some recognized examination it seemed to him that the only alternative was to insist upon so-called higher qualifications for those who joined the ranks of venereal disease specialists in future. It had happened in the Services, and it still happened in civil life, that there was a certain type of person who sought to enter this work because he or she regarded it as a quick and easy way to the status of specialist. Venereology was not an easy special subject, but some people had found an easy way into it. Unless there was some method of ensuring standards of ability and competence the service would be flooded out with people of inferior ability who lacked a proper interest in it.

Another point in favour of a special diploma was that a number of postgraduate students were coming to this country from the Dominions and elsewhere abroad to study this subject, and it was important for them to be able to take back some tangible evidence of the good work they had done.

Research work in venereology had lacked official support and had been left to the sporadic efforts of a few clinicians and pathologists who

were already fully occupied. It was important that research should be encouraged, and it was important too that there should be some centre or centres at which specialists and others should be able to revise their subject and bring themselves up to standard. For that purpose it seemed desirable that there should be a hospital in London or elsewhere which was entirely devoted to venereal diseases, staffed by a specialist staff and without competition for beds with other diseases and other special subjects such as existed in the large general hospitals. Most other subjects had special hospitals—neurology, cardiology, laryngology, ophthalmology, and so forth—and there should be a special hospital for venereal diseases.

Dr LEES endorsed what Mr King had said. They must put their own house in order and set a high professional standard for themselves. Too many people were creeping in trying to find an easy way to specialist recognition. A great many of them had the flimsiest knowledge of general medicine, still less had they a knowledge of diagnostic methods, epidemiology, and serology. Even if there were a course of training of not less than five years in venereal disease this specialty would still remain the Cinderella of Medicine.

Dr Lees felt they should stop as soon as possible the practice of putting general medical practitioners in charge of clinics. Many of these men had no interest in the work, and were not up to date, they took on the job for the guineas it brought, but neglected the clinic and left a great deal of the work to orderlies. The laboratory service had to be improved in many respects, and even in such distinguished laboratories as those attached to medical schools and universities it was unfortunately the experience that diagnosis, routine serology, and so on, was left to technicians or very junior members of the staff who changed fairly frequently. The venereal disease service had financed many of these laboratories to a large extent and was entitled to demand the high quality of service essential for the work.

Dr McELLIGOTT said that, when the Council asked Col Harrison to give this address, the date was put forward as far as possible in the hope that particulars of conditions in the National Health Service might be available. Though these conditions were still under discussion, it was known, at any rate, that the venereal diseases service was to be the responsibility of the Regional Boards. It was thus the responsibility of venerologists to do all they could to impress on these bodies the importance of the specialty, and by legitimate lobbying to interest colleagues in other specialties in the activities of this one. The Ministry had asked the advice of both Col Harrison and himself. This advice had been freely given, but to what extent it had been acted upon remained to be seen. He hoped that the venerologist of the future would concern himself not only with the diagnosis and treatment of the early and infectious stages of disease but also with its later manifestations, and that he would also interest himself in its epidemiology and social implications.

as well as in the prevention of its spread. If that was not a satisfactory life's work, he did not know what was.

Regional Boards would doubtless be acquainted with the general principles they would be expected to follow with regard to the various specialties, but as Dr. Lees had pointed out, it would depend to a large extent on the specialists themselves what impressions these recommendations made on the Boards. The problems of venereal disease were now very much before the public. When their incidence began to decline, as it inevitably would do, public interest would assuredly flag.

He hoped that it would be possible for regional advisers to be appointed. This did not mean that there should be a venereal diseases gauleiter in every region, but that there should be somebody whose duty it would be to inform himself on the activities of the specialty in the region and to whom the regional board could turn for advice. These advisers would be able to meet at stated intervals and a really useful exchange of views would be possible.

The Goodenough report had said that it took five years to train a specialist, and with this he agreed. The specialty would continue to be a 'Cinderella' if a high standard were not set. He himself had spent five years of his career in complete clinical isolation and knew from experience how undesirable this was. The idea of principal and subsidiary clinics being linked together was an excellent one, if only because it would do away with this clinical loneliness.

He agreed with everything that Col. Harrison had said about laboratory facilities and that a central reference laboratory was essential if there was to be anything like uniformity in results. If one man in every region made it his business to know something about the form of the laboratories in his region, then much could be done to keep the standard high. It was not difficult to know something about half a dozen serologists but quite impossible to know anything about a hundred.

Dr. Fairfield had spoken about economy. In many respects the venereal disease service had been a 'cut price' one. There were many clinics where medical officers had no access to a microscope, under such circumstances it was difficult to expect him to be keen. He was all against extravagance but necessary equipment and, indeed, conditions of service should be laid down on expert advice and should be constantly under review in the light of changing circumstances.

He agreed with Dr. Campbell about the importance of conferences. He knew little about the status of the Army venereologists, but in his experience in the Royal Air Force, the specialty had had a square deal.

What were the requisites of a good venereologist? First, he must be a good doctor; secondly, he must be keen; and thirdly, he must have devoted a minimal time (to which he had already alluded) to his specialist training. Possession of a diploma would be an additional advantage provided only that the examination was of a high standard and that the status of the examining body was likewise high.

He looked forward to the day when clinics for venereal diseases would be the responsibility of those who had made the specialty their life's work, and he considered that even today the opinion of a trained specialist should be obtainable free of charge by all who need it. He had succeeded to Col. Harrison's chair at the Ministry at a most important time, but his colleagues could rest assured that he was in complete agreement with what the Colonel had told them and indeed with the opinions of most of the other speakers that afternoon.

DR. BURGESS said that the National Health Service would provide a splendid opportunity for improving the venereal disease service but it was unfortunate that it would not be united. The Regional Hospital Boards would be responsible for the clinical side and the County Borough and County Council Health Departments would still be responsible for prevention. If liaison could be established between the clinical and preventive sides it would greatly improve the service. The same sort of thing would help in the social service. There would be almoners at the clinics and also social workers employed at the public health departments whose job it would be to deal with the notifications under Regulation 33B sent to the medical officer of health. If there could be some close link between the almoners and the social workers it would be a great improvement. Dr. McElligott had mentioned the question of a diploma and who should issue it. There was the only recognized Society for venereal diseases in this country, and a diploma issued by the Society would be of value.

DR. DAVID NABAPRO said he was a member of the Association of Clinical Pathologists which thought that clinical pathology would play an important part in the new service. It felt that higher qualifications were necessary and that five years' training at least was required before a man or woman could become a clinical pathologist. At a recent meeting they had discussed the question of the Association itself granting a diploma, and they concluded that if anybody were to grant a diploma in clinical pathology it should be themselves—who knew so much about the subject—rather than the Royal College of Physicians or Surgeons. He agreed that if there was to be a specialist diploma in venereology the M.S.S.V.D. should be the body to grant it.

The pathology in the past had been done very inadequately in a number of different laboratories and if that part of the work could be more reliably done in the future a great deal would be gained. As Dr. Fairfield pointed out, it was very important to the family and also to the State that a correct diagnosis whether positive or negative should be established. He was afraid that a number of pathologists did not realize its importance and the responsibility which was on them when they issued a report. If it were possible to get them to realize the importance of the results of their tests, much would have been gained.

The integration of social service with treatment and prevention was important, they should all, if possible, be under one director

LIEUT-COL J W EAMES speaking as one who had been the officer commanding several hospitals during the war, said that he had never relegated the venereal disease department to the worst part of the hospital, but had always done his best to help the venereologists attached to his hospital, and the same could be said of his confrères. In wartime, owing to expansion, one was bound to recruit bad as well as good material, and that often accounted for the work of some special treatment orderlies not being of as high a standard as might be desired.

With regard to pathologists, the fact that in wartime some had possibly not had much experience in serology was due to expansion, which inevitably necessitated this work having to be done in some cases by those who had not had the experience usual in peace-time.

DR HANSCHALL said that after Col Harrison's address it was perhaps natural for his audience to think of all the things in the venereal disease service that they had disliked, and to demand that they be now put right, and a listener to some speakers after Col Harrison could easily have got the impression that up to the beginning of the war 1939-45 the country had been very ill-served in the organized medical care of venereal disease. Such impression would be wrong, and proved wrong by consideration of the actual incidence of venereal diseases in this country up to 1941. It had been forgotten, apparently, that under the existing venereal disease scheme in this country, from 1921 to 1940 inclusive, there had been a great fall in the incidence of these diseases. In 1916, in the midst of the then world war, the first few venereal disease treatment centres for the civilian population were set up. This service in 1920 was expanded under the ægis and continuous guidance and advice of Col Harrison at the Ministry of Health—and the definite decrease in incidence began in 1921. The fall was especially, and significantly, in syphilis—significantly because it was only for syphilis that specific treatment, and specific serum test, were then to hand, and the essence and sovereign recipe for success of that scheme had been expert diagnosis and treatment in special centres, set up conveniently for that purpose. Moreover, the published promise of strict professional and civic confidence emphasized indirectly, yet properly and happily, that the treatment centre was for treatment and not for inquisition and telling on others. In fact, throughout the years up to 1941, in so far as incidence was concerned, this country had compared favourably with nearly all others and unfavourably with none, and that without any of those legal instruments of compulsion boasted for some other countries, and sometimes longingly boasted in this—with no better results whatever. The Armed Forces got their venereal disease, presumably, from civilians—and so much had it been reduced in our civilian population

that in 1940 the Army Consultant in venereal disease could tell them how very small was the incidence in the Army. Was anyone claiming it to have been larger in the civilian population?

—Of course, venereal disease services, like everything else, could have been improved—but he asserted confidently that those services could not have been all that much inadequate, ill-guided, manned with, so many of them, second-rate, part-time, medical officers, and yet have produced such good results. Either the results were phenomena unrelated to that still existing and now decried venereal disease service—and a venereal disease service was then a foolish waste of men and resources—or, if related, then that service had not been a bad one. Col Harrison was, indeed, to be congratulated on those results—a legitimate source of pride and satisfaction to him on relinquishing his onerous duties at the Ministry of Health, where, in the face of the great obstacles of civic and professional apathy, finding its ready excuse in financial stringency, he had managed uncommonly well in conjuring up and keeping alive the best venereal disease service of any country, with, at any rate up to 1941, not one medical boss and not one policeman in it. Its ideals and principles, chief of which had been professional freedom in adequate treatment centres, under strict confidence, should be maintained and fostered.

DR MASCALL said he would like to see a return to the time when all clinics were under inspection, because he felt sure that if a medical officer was running his clinic on proper lines he would not fear inspection, in fact he would welcome it. He remembered that when this was the custom one did not know when the inspector would arrive and so one was kept on the alert. At that time he was absolutely isolated, and there was nobody with whom he could discuss professional matters and difficult cases. It was a help, however, to know that certain standards were expected, and to try and improve on them. He was convinced that, if the future service was going to improve the standard of work in the field of venereology, it would be essential to have a senior specialist in every region to keep his eye on what was going on in the various clinics in the district. He thought that a considerable amount of opposition would come from the medical officers of health who would not like losing their part-time venereal disease officers. The average M O H was not interested in venereal disease, which was rather an irksome sideline.

He had had experience of a combined appointment and it was most unsatisfactory. As maternity and child welfare officer, smallpox officer, and occasional meat inspector, as well as venereal disease officer, he had not uncommonly been called to a confinement or something else urgent in the middle of a venereal disease session, and this call usually ended the session as there was nobody else to carry on. It was unfair to the patients who had often come from a distance. The leave question was also a problem. When he went on leave a general practitioner, who

admitted that he had had practically no experience of venereal disease work was brought in to carry on. Before he departed he had to go through all the current cards and write down for the locum in pencil what had to be done. These instructions if carried out were filled in in ink on his return. It did not help towards a peaceful leave.

He would like to support strongly the idea of a Diploma in Venereology. Many doctors dabbled with the specialty for years but really had only a very superficial knowledge of the subject. It was possible for a person to complete the specified 130 hours in a clinic and yet at the end of it to know practically nothing. He thought that an examination would test the knowledge and experience gained during the period of tuition and so tend to raise the standards of venereology. Whether this Society without the support of the Royal Colleges or some other examining body was weighty enough to issue a diploma he was not sure.

MAJOR SCOTT had seen a number of trainees who were merely content to learn the basic principles of the subject and spend the minimum amount of time in a venereal disease clinic before moving on to the fields of medicine and surgery, which they appeared to think were worthy of more time and labour. On one occasion a trainee asked him what he should read and when he mentioned works by Harrison, Pelouze, and Stokes he was informed that books such as these were much too comprehensive and would not be a study of the *Aids to Venereology* be quite adequate to achieve the standard of a graded venereologist. This he thought was a fair reflection of the interest they had in venereology.

Contact investigation was very important, but a great number of doctors thought it was not the sort of thing they should have to do. When abroad he had often the full responsibility of having to visit venereal disease contacts and persuade them to have treatment. This was of course impracticable at home and in any case welfare workers and almoners had the matter well in hand.

The liaison between the pathologist and venereologist was more important than ever now that more blood tests were being performed. He found a great deal of his day taken up in studying difficult serological problems with the pathologist and it was only by each taking a sympathetic attitude to the other's problems that good and accurate results could be obtained.

DR. C. S. NICOL said he agreed with Mr King and Dr Lees on the importance of having a definite policy rather than a discussion within these four walls only, if the study of venereal diseases was to be a specialist branch of medicine. Dr McElligott had said that negotiations were still going on and although the decision about a diploma was difficult, he felt that one granted by the Royal Colleges would carry more weight. He did not think they could decide on that point immediately, but it would help their cause in

general if the Council of this Society issued a statement of suggested qualifications for a specialist in venereology. Although nobody agreed that it was the right standard the attendance of 130 hours at a clinic was the current standard and it might be very helpful if some statement was made by the Council in the first place including their views about a diploma.

He very much disagreed with Dr Hanschell's suggestion that venereology could be efficiently practised as part-time work. In any other subject the specialist was not part-time in his specialty. Dr Mascall had given his experience of what could happen in a clinic: they did not want that sort of thing to happen in future. However keen a part time specialist might be he could not do such good work as one who devoted all his time to the subject.

DR JACOBSON said that some of the points brought back memories of the problems considered many years ago in pre Hitler Germany and which seemed to be the same in every part of the world. In Germany the Venereal Diseases Society was not quite the same as the Society here because it included eminent law,ers sociologists and people who were generally interested. It gave a great impetus to public awakening to the necessity of controlling the spread of venereal disease.

Mr King did not speak only of the necessity for a diploma, but asked also for a specific venereal disease hospital in London, and that, he thought, was of the utmost importance. The Society should see to it that there should be created properly equipped venereal disease clinical departments in the teaching hospitals where every facility for research would be given. If they did not have venereal disease departments with beds attached as in many other countries venereal disease clinical research would be impossible and it would not be possible for a young and new generation to be trained as specialists. He thought it was necessary to have five years' training, one of which should be devoted to V.D. pathology. In other countries the serological department was under the charge of the V.D. specialist and he did not see why that should not be so here. Also the pathologist could work in the V.D. department to see the way in which laboratory results were interpreted, and thus he would understand the necessity for and the importance of the serological work.

With regard to part time specialists in 1928 in Germany, medical officers of three to five years' experience in venereal disease were given the appointments. When the evening clinics were set up these senior assistants had to devote two or three evenings a week to the venereal disease clinics where they did very good work.

COL HARRISON in reply thanked the members for the kind way in which they had received his suggestions. He was particularly thankful to Dr Hanschell for relieving the gloom in respect of the service as it existed at present. He agreed that in their anxiety for reform they had overlooked the

good points of the existing service. Undoubtedly the rates in the Services during the war testified to the cleanness in respect of venereal diseases which had been achieved here in the years between the two wars, and much of the credit for that was due to the present service with all its imperfections. He would like to emphasize that they should be unanimous with regard to the establishment of regional consultants, and also on the principle of headquarters and subsidiary centres, if they could say that they would give nobody any peace until they had those, much would be achieved. He did not suppose that all the centres would be staffed at once with medical officers who were primarily specialists in venereal disease, but if they had regional consultants these would prevent much of that feeling of loneliness and isolation which he and many other speakers had mentioned. Unfortunately the Local Government Act of 1929 put an end to routine inspection of clinics, and he hoped that, under the National Health Service they would get back to some more intimate association of the Ministry's Adviser and other workers in the venereal disease scheme.

He thought that the regional consultants could probably be well worth their keep by preventing waste. In the early days of his appointment at the Ministry he was very depressed over the operation of "The Geddes Axe". At that time he put up a proposal for a scheme of reorganization of the venereal disease arrangements which would cost an extra £40,000 a year, and he was told that he could not get 40,000 pence. He thought seriously of resigning because he did not see how they could carry on without the reorganization. Then he thought that perhaps he could save that £40,000 by looking into the expenditure. He did so, and by pointing out to local authorities and venereal disease officers how they were wasting money in various ways that were useless to patients, a great deal more than £40,000 a year was saved,

in fact, he calculated that that sum was saved on drugs and dressings alone (extravagance in placebos, fancy packings, lavish dressings, and so on). A regional consultant would be worth his keep on this count alone.

Apart from that it was impossible for an adviser in Whitehall to supervise all the centres in the country. He used to calculate that it would take one man three years to visit them once. The visit should be made by someone practising in the specialty, the purely office inspector cut no ice with the venereal disease officer, but according to his experience the practising consultant was always welcome.

Mr King had suggested that there should be a special hospital for the training of specialists. In the Army long ago, when the Army Medical Service was reformed after the South African War, the late Col F J Lambkin had worried the War Office, until in 1909 he got a hospital established for the training of the Army venereal disease specialist, he (Col Harrison) was one of those who trained the specialists there. He thought he could claim that the candidates did know something useful about venereal disease, including its pathology and the laboratory tests, by the time the course was finished. There was a lot to be said for a special hospital, whether it would be possible to get civilian patients of the right kind to go to such a hospital, he did not know. If a diploma on five years' training was wanted, arrangements must be made for something in the meantime.

With regard to the points raised by Dr Burgess he thought that the regional consultant should be the person to co-ordinate the work on the public health side with that on the diagnostic and treatment side.

He would like to think they were leaving the meeting resolved not to give anybody any peace until they had got established in the new service the principles upon which they were agreed.

# THE MASKING OR DELAY IN THE DEVELOPMENT OF SYPHILIS AFTER PENICILLIN THERAPY FOR GONORRHOEA\*

BY

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## Immunity in Syphilis

The discovery of penicillin by Sir Alexander Fleming and its development by Sir Howard Florey was without doubt one of the greatest advances of medicine, and yet a few years experience has shown that even this great bequest to humanity has not been an entirely unmixed blessing.

Laboratory trials soon showed that the gonococcus, the *Treponema pallidum* and other organisms, were sensitive to this new drug. Clinical tests also showed that, unlike previous similar substances, a dosage tolerated by man still had a lethal effect on penicillin sensitive organisms in the body. This finding, although a blessing in many ways, confronted venereologists with an entirely new problem in therapeutics, and the danger of suppressing or modifying the development of syphilis by using the new drug for the treatment of gonorrhoea in a dosage adequate for the latter but inadequate for the successful treatment of syphilis was immediately apparent. This problem has worried many clinicians who, while appreciating the numerous advantages of penicillin treatment for gonorrhoea, are now looking five or ten years ahead and wondering whether they will then be confronted with a sharp rise in incidence of the late complications of syphilis, and especially of neurosyphilis.

The natural history of syphilis as a disease is of great interest, and there are certain aspects which are as yet imperfectly understood. The clinical development of the disease in its first few months in the untreated case is too well known to require description here, but there are even during this period certain phenomena that are difficult to explain.

Immunity in syphilis is a subject of great interest which has never been satisfactorily explained, and Chesney (1927), in his admirable monograph on the subject, surveys it thoroughly. He described how rabbits and monkeys, after experimental infection, may in some cases be found to harbour treponemata in their internal organs or lymph nodes and yet to show no clinical sign of disease and to have a negative serological test. Whether a previously uninfected body has any natural immunity to the disease is hard to say. The presence of antibodies in the body as agglutinins, precipitins, or opsonins has never been conclusively proved, and there is little evidence to suggest phagocytosis, but Bergel (1925) (quoted by Chesney) claims in experimental work on rabbits to have demonstrated active phagocytosis of treponemata by large lymphocytes or mononuclear cells. This important finding, however, has not been confirmed and was only found in certain stained preparations. That both rabbits and humans develop during an attack of syphilis a strong resistance to a second primary infection has been demonstrated beyond doubt experimentally and clinically, the exact nature of this immunity has not been determined. There appears to be no rise in circulating antibodies but rather an alteration in the tissue response to a second inoculation. Kraus and Volk (1906) (quoted by Chesney) suggested this acquired immunity might be regional, and the former considered the skin to be the chief site of this immunity. Brown and Pearce (1921), experimenting with rabbits, found that there was an inverse ratio

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between the initial response to syphilis inoculation and the subsequent course of the disease, and they formulated a "law of inverse proportion"

Chesney and Kemp (1925) showed that a second infection in the rabbit may show no local lesion—a fact which they attributed to local change—and yet may cause a blood-borne infection, this fact suggesting that other tissues have not developed this high immunity. The variations in the activity of the disease in its different stages have been explained by two hypotheses. The first, that the *Treponema pallidum* has a complex life cycle with varying powers of invasiveness, has now for the most part been abandoned in favour of the theory of some allergic alteration in tissue response to the treponema.

Morgan (1939), in his experimental work with rabbits, used special suspensions of treponemata in varying concentrations and was thus able to inoculate rabbits with varying strengths of inoculum. He made the significant discovery that when a minimal number of treponemata were used no local lesions were produced, and subsequent observation with serological tests and post-mortem examinations showed no signs of a syphilitic infection, employing rather larger numbers, he again found no lesions at the site of inoculation but subsequently the animals developed positive serological tests, in a third group with still larger numbers he demonstrated both the typical clinical picture of experimental syphilis and a local lesion at the site of inoculation. Subsequently he was able to show that an inoculation of less than 30,000 treponemata in a rabbit did not produce any local lesions but did cause a generalized infection with a positive serological test. He suggested that the same results were likely to be found in naturally acquired syphilis in man. In considering this it must be remembered that the skin and mucous membranes in rabbits are not so susceptible to local lesions as those in humans. Morgan observed that statistically syphilis in the early stages of the disease was, in America, commoner in men, who out-numbered women in the proportion of about 2:1, while treatment of the late complications of the disease showed that women patients formed 53 per cent of the total. He went so far as to suggest that, in his experience, half the patients who were under treatment for severe late complica-

tions such as cardiovascular syphilis or neurosyphilis had had no signs or symptoms in the early stages. The healing stages of the chancre and the disseminating secondary syphilis are accompanied by massive destruction of treponemata by some agency unknown, and the disease is frequently then restricted to an inactive local form. He considered that inadequate treatment of syphilis in the early stages might interfere with this natural tendency to localize the infection into a relatively innocuous form. He claimed that such inadequate treatment raised the incidence of serious late complications in syphilis by some 10 or 15 per cent.

### Boeck's Experiment with Untreated Syphilis

The greatest experiment of all time in untreated syphilis was carried out by Boeck in the years 1891 to 1916 at his Oslo clinic. He maintained that iodides and mercury, the only remedies of his day, were symptomatic remedies which not only failed to eradicate the disease but paralysed the body's natural defences, leaving certain parts, especially the central nervous system, vulnerable to the organisms. During the stated period he saw 2 181 patients who were diagnosed clinically as suffering from syphilis and who received no treatment from him, the possibility that some of them received treatment elsewhere cannot be entirely dismissed. In 1929 at a discussion in Oslo on these cases Bruusgaard and Dahlstrom, two former pupils of Boeck, gave some very interesting figures of the results of this treatment, or rather lack of it by Boeck. At this discussion Bruusgaard disclosed that he had managed to examine 309 survivors of Boeck's original group and obtained clinical or post-mortem findings on 164 who had died since having originally been seen and diagnosed. All the living patients were given a thorough clinical examination, and had their hearts radiographed. The majority were tested serologically, and the cerebrospinal fluids of a few were examined. Of the 164 who died, the majority had died in Oslo hospitals, the cause of death being known and complete post-mortem examination having been performed on 40 cases. Of this total of 473 cases thus re-examined more than twenty years after their initial untreated infection, only 37 per cent had developed any active lesion of late syphilis, 14 per cent showed a positive sero-

logical reaction but no other signs of the disease, 22 per cent had died from other causes one half of these cases over a period of twenty years had developed no obvious lesions of syphilis, and 27 per cent showed clinical arrest or spontaneous cure and gave a negative serological test. Approximately 14 per cent were suffering from cardiovascular disease, 2.5 per cent contracted general paralysis of the insane, and just over 1 per cent were found to have tabes. As, however, all the cases of general paralysis of the insane in Oslo over this period had been carefully separated for hospital treatment, it is reasonable to suppose that this figure represents the number of such cases developing from the original 2,181 patients rather than from the 473 Bruusgaard was able to find, and therefore this figure may more accurately represent a percentage of 0.6 per cent. Dahlström pointed out at the same discussion that this last figure compared very favourably with the usual percentage after treatment, which he estimated as 4 per cent. He also stated that in his psychological clinic he had very few G.P.I. cases which had been under Boeck's treatment but he had seen a considerable number which had received mercury or iodides. Discussing the two G.P.I. cases of Boeck's which he had seen he suggested that they also might have been given these drugs by other doctors whom they had visited. He drew an analogy with the rarity of G.P.I. among tramps and negroes, other than those of the latter who lived in large cities where treatment for syphilis was readily available.

Stokes and his fellow workers (1934), in a survey of the accomplishment of treatment in early syphilis, compared their records after treatment with Bruusgaard's figures. In cardiovascular complications they found an appreciable improvement in their figures as compared with Bruusgaard's. The greatest discrepancy in their two analyses is that of late skin, mucosal, and bone syphilis, where Stokes's percentage in the 3 to 10 year group was 1.2 per cent, while Bruusgaard's was 31.7 per cent. This finding is of interest in connexion with Brown and Pearce's (1921) theory of the protective influence on the rest of the body of skin and mucosal manifestations of syphilis. It must be remembered that Stokes's figures are those of adequately treated syphilis, the untreated patients of Boeck's series whose skin manifestations were not treated symptomatically

in any way seem to have been protected surprisingly well from neurosyphilis. How much that protection would be interfered with by modifying the early manifestations of syphilis is a matter for thought, the available evidence suggests that these skin manifestations are a vital factor in natural immunity. Stokes compares some results of inadequate treatment favourably with Bruusgaard's but admits that by inadequate treatment he means cases having had less than twenty injections of arsenic in some form. He does not include a series of patients who have had one or two injections only of this drug which would be analogous to the critical point in this paper and which might have interfered with the cutaneous manifestations of the disease without being in any way likely to destroy all the organisms present in the body.

#### Inadequate Arsenical and Penicillin Treatment

Statistics showing results after entirely inadequate arsenical treatment are naturally not much in evidence, but Kemp and Menninger (1936) reviewing the subject suggested that the frequent early development of late complications of the disease could be attributed to inadequate treatment in the early stage. There are grounds for belief that the actual incidence of these late complications is also raised by such treatment. That a similar phenomenon may be found with penicillin is suggested by Cole and his fellow workers (1946). They treated a series of 31 cases of syphilis in the primary or secondary stage with 1,000 units of penicillin given three-hourly for seven days, thus giving a total of 56,000 units. They report that 13 of these cases relapsed within one year, and of these 5 are described as 'neuro-relapses'. A further series of 81 cases were described which were given a total of 300,000 units similarly spaced. In this series they report 26 relapses within one year, among which were 10 cases of neurosyphilis. Unfortunately they give no further clinical details of these cases. Although no true comparison can be drawn between such protracted treatment and single large doses or treatment spread over a few hours, these results are disturbing and it must be remembered that Kemp and Menninger (1936) showed that the earlier the inadequate arsenic therapy was given the greater was the likelihood



of the early onset of late complications of syphilis. The potential danger of penicillin treatment in a dosage insufficient to cure syphilis during the possible incubation period of this disease seems on these findings alone to be very real, and yet no such cases have been reported in the literature and I have heard of no such cases of this type. The time, however, is yet early and we cannot dismiss this possibility lightly.

It has already been pointed out that Kemp and Menninger (1936) showed that inadequate arsenical treatment, while apparently curing the obvious visible signs of syphilis in the early stages, may very considerably shorten the period of latency before symptoms and signs of later complications, especially neurosyphilis, develop, it is also likely, although not universally accepted, that the incidence of late complications is greater after inadequate arsenical treatment. This possible danger is chiefly apparent during the early stages of the disease, when arsenic may destroy the treponemata in the skin lesions which are provoking extensive specific antibody development, and thus may diminish the latter and interfere with the host's development of specific immunity without destroying all organisms in the body. Inadequate treatment given later appears to have little effect on accelerating complications, as by then the body has developed its own immunity which cannot be altered by any treatment. In view of these findings the theoretical danger of inadequate treatment during the incubation of the disease is a matter requiring the most careful consideration, while it is accepted that experimental syphilis in the rabbit is curable by one large dose of arsenic, no such uniform result could be expected in man as the dose required would be too toxic. Furthermore it is acknowledged that syphilis in the rabbit is a condition more readily cured than in man. Whether a single massive dose of penicillin could ever cure human syphilis is a problem that cannot be solved definitely for years to come.

### Syphilis d'Emblée

Syphilis d'emblee is a term used sometimes rather freely but often imperfectly understood, possibly, as Lane (1912) suggests, cryptogenic syphilis would be a more satisfactory name for this phenomenon. Pernet

(quoted by Lane) suggested that the condition was merely syphilis in which the primary lesion was so insignificant as to escape the notice of both patient and doctor, and that therefore the condition did not in fact exist as a separate entity. Lane, however, quoted six cases of his own, in none of which was it possible to demonstrate the site of entry of the organism, and all of whom developed a virulent form of invasive syphilis which, with the limited armamentarium of therapeutic agents of those days, was exceptionally difficult to control. He also quoted two cases described by Jullien and several described by Walsch in which, although the site of entry of the organism was known, no local lesion developed at this site but a generalized infection of a secondary type of syphilis became evident at an early stage, this frequently being of a particularly virulent type. Lane, in discussing these cases, points out that the absence of the initial localized skin lesion appeared to be associated with an unusually virulent type of generalized syphilitic infection, and he endeavoured to explain this on the well known principle, particularly evident in his day of limited effective chemotherapeutic agents, that the earlier treatment was begun the more satisfactory was the prognosis and the less virulent were the subsequent stages of the disease.

It is possible that Brown and Pearce's law of inverse proportion may have been the important factor affecting the condition, namely, the absence of localized initial skin lesion, by which the immunity of the body as a whole to the invading organisms would be considerably below that found in cases with skin lesions in which specific antibodies are presumably being formed.

Boeck's work in Oslo and Bruusgaard's subsequent observation, have already been mentioned, and in the cases that Bruusgaard (1929) managed to examine subsequently the relative absence of any severe complications of untreated syphilis is hardly in accordance with Lane's explanation.

### The Present Study

In this paper an attempt is made to survey the relevant literature, to consider the theoretical possibilities, and to endeavour to correlate them with the clinical histories of the cases described here and elsewhere.

That the use of penicillin was likely to lead to the masking or delay of the initial or primary lesions of syphilis was recognized by all venereologists as soon as this treatment became available for general use. In 1945 Lydon and Scott Cowe emphasized this danger and suggested that gonorrhœa should be treated with 2,000,000 to 3,000,000 units to cure the potential syphilitic infection as well, an alternative suggestion was made by these authors that gonorrhœa treated with penicillin should be kept under observation for two years with serological tests. Other writers followed with suggestions for shorter periods of observation. It is suggested that in the present state of our knowledge it is too early to be dogmatic on this very important point, too few cases have so far been reported to allow a sound reliable opinion to be formed.

In this paper a short series of cases which has been collected over a period of about eighteen months is presented, all but one of which have been seen and treated personally, some of these show an incubation period considerably in excess of any reported up to the present, so far in excess, indeed, that one is tempted to accept the easy explanation of a subsequently acquired syphilitic infection after the initial gonorrhœa. These patients have, however, been carefully interrogated and the significance of their statements explained, and as far as it is ever possible to be certain of a patient's history I believe these histories to be correct, I share the view of many venereologists that patients well handled are generally very truthful, especially if they can be made to realize that such truthfulness is in no way to their disadvantage. The total number of cases from which these are selected was in the region of 6,000, of these, naturally not all were seen personally but case records have been examined, any relevant patients examined and questioned and all doubtful cases discarded.

Destructive criticism of facts and records that do not accommodate themselves to an accepted view is often easy, and Cronin (1947) in his criticisms of Batchelor's and others (1946) cases, appears to fall into this error. We must recognize that new facts may come to light altering existing conceptions, such ideas must be examined critically, and if they are substantiated some reorientation of our existing views on the subject may be

required. I find it surprising that venereologists who as a whole are noted for their critical and almost sceptical outlook, have accepted with surprising complacency, within a period of months after the introduction of penicillin treatment for gonorrhœa, the principle of a routine six months surveillance period of patients after penicillin treatment for gonorrhœa.

#### Animal Experiments of Magnuson and Eagle

Some very valuable animal experimental work in this subject was carried out by Magnuson and Eagle (1945), who prepared a centrifuged emulsion of syphilitic rabbits testicles, thus separating the *treponemata* and diluted this preparation in varying proportions so that an accurately regulated inoculum could be injected. The injection was carried out intradermally at different sites in varying concentrations, they used a large number of experimental animals which were given a single injection of penicillin the dose employed being about 1/32nd of the estimated amount required to cure rabbit syphilis and estimated to be equivalent to about 120,000 units in man. With a small inoculum of *treponemata* and penicillin given on the third day after inoculation, only 1 per cent of the experimental animals showed lesions in which *treponemata* could be detected on dark-ground examination, whereas, using the same inoculum without penicillin, 75 per cent showed lesions in which *treponemata* were detected. When penicillin treatment was delayed until the tenth day after inoculation, no *treponemata* could be detected in the lesion for the first thirty days, but they were subsequently found there. One case was reported in which penicillin was given on the fourteenth day after inoculation with *treponemata*, after which a lesion, in which *treponemata* had been seen quickly became free of live *treponemata* and in a few days had healed, careful observation showed no subsequent sign of relapse. Although manifestations of syphilis were delayed, these authors reported no cases of an asymptomatic infection after penicillin, but recorded that some lesions were insignificant and might well have been missed except on very careful examination. Summarizing their results they stressed the importance of two factors in the suppression or delay of the primary syphilitic lesion. These were the total number of

treponemata inoculated, and the stage at which penicillin was given, they demonstrated conclusively that the earlier the penicillin was given the greater was the likelihood of delaying or suppressing the lesion. From their findings they suggested that human syphilis might sometimes be aborted by early treatment with penicillin, and went so far as to suggest the use of penicillin prophylactically, the very serious danger of such a step, however, must be obvious in our present state of knowledge, and fortunately there is no record of this having been done clinically.

### Other Rabbit Experiments

Further important experimental work with rabbits was described by Eagle, Magnuson, and Fleischman (1946), who demonstrated that a constant low concentration of penicillin in the body over a longer period was a great deal more effective in curing experimental syphilis than a massive concentration over a short period. They demonstrated that the number of injections given to an experimentally infected rabbit over a fixed period of treatment showed an inverse ratio to the total curative dose of penicillin required. By increasing the frequency of injections over that period a smaller total dose of penicillin was required to cure syphilis in the rabbit, they found that, when the number of injections was decreased, more penicillin was required during that same period to effect cure.

Comparing curative effects of penicillin and mapharside in rabbits, weight by weight, the former was ten or twenty times more effective in the rabbit, but in the human subject they estimated penicillin to be only two to four times more effective by weight.

These findings were confirmed by Carpenter and others (1946), who inoculated rabbits intratesticularly with a suspension of treponemata, six weeks later they started intramuscular penicillin treatment, and they found that the equivalent of 3,500,000 units in man given in a single dose did not cure the condition, the same or even a smaller dosage given over 16 hours did frequently cure the disease, and if this period of treatment was extended a smaller total dosage was required. By the time they started treatment, however, a widespread dissemination of treponemata must have taken place. In both these articles the relative ease with which

rabbit syphilis can be cured as compared with human syphilis was stressed.

The results reported by Cole and others (1946), already described, although not comparable with results from single massive doses or a dosage spread over a period of 24 to 48 hours, cannot lightly be disregarded, and it is obvious that the dangers of undertreatment with penicillin are very real, the effect of inadequate arsenic therapy on the activity of the treponema has already been described. These figures would suggest that penicillin has at the very least an equal effect if given in quantities insufficient to effect a complete cure, in view of its more rapid destructive effect on the organism, it may well be that the effect of undertreatment of syphilis with penicillin is even more serious, as there is less chance for the skin to develop specific antibodies and provide the body with some immunity. When penicillin is given sufficiently early to abort all skin lesions and yet not in sufficient dosage to destroy every organism in the tissues, the body may be deprived of any chance of acquiring immunity and if any organisms are still present the whole system would lie defenceless before them when they subsequently developed and multiplied.

### Dual Infection

Examination of the literature on this subject shows that less than 100 cases of dual infection have been described with full details, and as with one or two exceptions the incubation period is less than 90 days the conclusion has been drawn from these entirely negative findings that the incubation period does not in fact exceed 90 days. Accumulative evidence of a negative nature over a long period, combined with the absence of any contradictory reliable positive evidence, would suggest that such a theory might well be true, but it is considered too early in the present instance to accept this hypothesis, and although the cases quoted in this paper are few in number, I consider it to be in the best interests of veracity to try thus to check this complacent attitude.

### Other Literature

Fromer and others (1946), after drawing attention to the febrile reactions sometimes seen after penicillin treatment for gonorrhoea and suggesting that these are Jarisch-Herxheimer reactions, suggest that when

penicillin is given during the incubation of syphilis the disease may first manifest itself as a delayed generalized cutaneous syphilis without any localized lesion at the site of entry. They advise that cases should be under observation for four months after their initial treatment for gonorrhœa with penicillin. They found that Jarisch-Herxheimer reactions develop within eight hours of the penicillin injection, and are found in 90 per cent of such cases in which syphilis is present but not yet evident as a chancre or rash. Cole (1946) and his fellow workers' results of the treatment of syphilis with small doses of penicillin must be considered to be of great importance in spite of their rather vague definitions of the relapses. Although the relatively small number of cases described make them of limited value from the statistical point of view, this series of Cole does reveal the danger of undertreatment of syphilis with penicillin, suggesting that while the usual interval to the serious late complications is decreased, their incidence is increased. With the results shown in Cole and others series it is unlikely that anyone will wish to repeat this work in humans. They, like other workers, found that within 12 to 18 hours of the administration of penicillin no treponemata could be found in any of the superficial lesions.

Reports of cases relevant to the subject of this paper on the whole show a very similar picture with some delay in the diagnosis and an attenuated form of the primary and secondary stages of the disease.

Van Slyke and Steinberg (1944) describe two series of cases of gonorrhœa that had relapsed after sulphonamide treatment. These were given penicillin injections intramuscularly, in their first series, comprising 114 cases, the patients received 80,000 units over a period of twenty-four hours. In their second series, comprising 65 cases which received 125,000 units over a period of  $7\frac{1}{2}$  hours, two of the patients had penile ulcers in which no treponemata could be found the day after treatment, three weeks later, however, both patients had positive serological tests. The authors concluded that early treatment with penicillin could mask the primary stage of syphilis entirely and recommended dark-ground examination of any suspicious lesions before penicillin administration, and careful observation of the patient subsequently—

after describing to him the nature of an expected further manifestations.

Baier and Pincus (1944) describe one case of gonorrhœa treated with 100,000 units of penicillin two days after a tiny sore was noted on the penis. Repeated dark-ground examinations of this sore were negative after penicillin therapy, and it eventually healed fourteen days after appearing, six weeks after the penicillin treatment. Serological tests were strongly positive for syphilis. From this the authors concluded that penicillin might destroy or assist in destroying treponemata in the localized skin lesion.

Osmond (1945) reports a case of gonorrhœa treated by two-hourly injections of 20,000 units of penicillin, giving a total of 100,000 units. Subsequently a small ulcer developed on the shaft of the penis, but all attempts to demonstrate the presence of treponemata failed and serological tests were negative. Later this lesion healed, but further ulcers developed in which treponemata were found. This occurred on the eighty-second day after the initial exposure to infection, and serological tests at this stage were still negative.

Canizares (1944) describes one case of gonorrhœa treated with 50,000 units of penicillin. A papular lesion present on the penis at that time was examined without result for treponemata, it then healed, but recurred ten days later, when treponemata were present. Horn and Dakin (1944) cite a case of gonorrhœa, resistant to sulphonamide treatment which was given 5 injections of 20,000 units of penicillin in aqueous solution, 34 days later 52 days after exposure, a small ulcer developed in which treponemata were found.

Scott Cowe (1945) reports a patient with gonorrhœa treated with 100,000 units of penicillin who later developed a sore in which treponemata were found, the incubation period from exposure to diagnosis was 62 days.

Lydon and Scott Cowe (1945) reviewed the effect of systemic penicillin treatment of skin lesions—which has already been described in this paper—but claimed that penicillin was dangerous to use in the treatment of syphilis except in the very early stages, and then should be used only in large doses, as penicillin does not reach the cerebrospinal fluid to any extent and 50 per cent of cases of generalized secondary syphilis do show involvement of this fluid. Subsequent findings by other workers do not

confirm this statement, and Stokes (quoted by Willcox, 1946) considered that penicillin was effective in all types of neurosyphilis and that the most striking effect was on the cerebro-spinal fluid. Lydon and Scott Cowe described two cases, one of which illustrated the usual finding of a clinical chancre which on bacteriological examination after penicillin treatment was negative. Subsequent serological tests were positive. Their second case was of gonorrhoea resistant to sulphonamide therapy. The patient had round the fraenum an indurated oedematous lesion which looked like a chancre, but bacteriological confirmation was not found. After 100,000 units of penicillin, given over ten hours, this suspicious lesion vanished and at the time of the report had not reappeared. The patient was, however, under observation. They ask the question which has not yet been satisfactorily answered, "Does incubating syphilis inadequately treated give rise to an early incidence of the normally late serious complications of syphilis?" They suggested treating all gonorrhoea cases with a dosage of about 2,500,000 units of penicillin, which they at that time considered adequate to cure syphilis, as an alternative they proposed that all penicillin-treated cases of gonorrhoea should be kept under observation for two years.

Atcheson (1945) describes a case in which a maculopapular rash developed within fourteen days of the injection of 100,000 units of penicillin.

Lloyd Jones and others (1946a) reported a series of 617 cases of gonorrhoea treated by injections of penicillin in saline over a period of eight hours, the total dosage was 100,000 units. All patients received serological tests at three and six months before being discharged. The authors claimed that in the ten double infections recorded syphilis was manifest within the accepted period of time. In another paper in the same year (Lloyd Jones and others, 1946b), the same authors described another series of 250 cases of gonorrhoea, of whom ten developed syphilis after similar penicillin treatment to those of the first series. In this series also they claim no delay in the incubation period. None of their cases was observed, however, after six months, and no one is to know whether any of these patients subsequently developed a syphilitic infection. Case 1 of the series in this paper is doubtless

shown in some similar records as an uncomplicated case of gonorrhoea.

Hailey (1944) reports a case of gonorrhoea treated with sulphonamide which developed a small penile sore, repeated bacteriological tests for this were negative, and 100,000 units of penicillin were given for the gonorrhoea, 69 days after exposure the sore recurred, still devoid of treponemata, but at this stage the Kahn reaction became positive.

Cronin (1945) suggested that cases considered in this category should have two important qualifications. There should have been no further exposure to venereal infection after the development of gonorrhoea, and the history should suggest a genuine double infection. He reported 183 cases of syphilis of which ten had been genuine double infections after receiving 100,000 units of penicillin for gonorrhoea. He states that within two months all showed chancres in which treponemata were demonstrated. He also considered that this dose of penicillin did not prevent serological tests becoming positive within the normally expected period.

#### Syphilis Obscured by Local or Systemic Penicillin

The same author (1946) describes seven cases of great importance but not strictly relevant to the subject of this thesis, briefly, these were all cases in which syphilis in some form was not initially recognized but the condition was treated empirically, as unfortunately occurs not uncommonly, with penicillin. One case of secondary syphilis was diagnosed as tonsillitis before the skin eruption was obvious, and when the latter did appear it was diagnosed as a sulphonamide-sensitive rash and penicillin was given instead. Once penicillin has been given in such cases, and others such as undiagnosed digital chancres the diagnosis of syphilis may be very difficult for even the expert to prove, penicillin cream in a like manner will destroy all treponemata in a skin or mucosal lesion for some days. The importance of the general practitioner's realizing the significance of such cases cannot be over-stressed. Cronin again (1946) reports a further series of five cases in which the diagnosis was obscured by the use of penicillin locally or systemically, he also makes three wise suggestions: serological tests should be carried out before giving penicillin for any

condition, the whole body should be thoroughly examined at the same time for the evidence of a primary syphilitic lesion, and a temperature and pulse chart should be kept while the patient is under treatment with penicillin, the possibility of any otherwise unexplainable rise of temperature and pulse being a Jarisch-Herxheimer reaction would have to be considered. These suggestions, although excellent in theory, would present formidable difficulties, and with penicillin now available for general use by all practitioners it is unlikely that such advice would receive universal support. The suggestion that a patient might have venereal disease has to be made very delicately, and I doubt whether every patient having penicillin would submit to such investigations or management.

Batchelor and others (1946) report seven cases of double infections after penicillin treatment, with incubation periods varying from 39 to 184 days. It is significant that even in their short series the syphilis manifested itself in three different ways, two patients were serologically positive, three showed treponemata present in chancres, one developed characteristic secondary syphilis, and one showed a positive serological test combined with treponemata present in the primary lesion. Cronin, discussing this series, dismissed the incubation period of 184 days as improbable because the 'domestic situation' of this patient suggested that his story was unlikely to be true. From the case history in the original paper there appears to be little evidence on which to base this statement and I have already discussed the question of veracity in venereal patients. I think that the most experienced venereologists agree that in time the truth is obtainable from most patients with venereal diseases. Batchelor and others suggest on their findings that a three months observation period is insufficient and make a plea for sulphonamide therapy for pregnant women suffering from gonorrhoea.

Cronin (1947) reviews previously reported instances of double infections with delay in the development of syphilis and describes a further 19 cases observed by himself, with an incubation period within the usual limits of syphilis, after receiving 100,000 units of penicillin for gonorrhoea. He noted that the first clinical lesion usually developed about four to six weeks after the penicillin treatment, suggesting

that the treponemata surviving the single massive dose of penicillin act as a fresh inoculum. Included in Cronin's series is one showing an incubation period of 152 days which he apparently ignores when he claims that no cases with negative serological tests at three months subsequently became positive.

A recent personal communication from Erskine (1947) is of interest and possibly of significance. He reports that during the last twelve months he has treated four pregnant women who were found to have positive Wassermann reactions at ante-natal clinics. In each of these cases, the husband who had been in the Armed Forces had previously had penicillin treatment for gonorrhoea but routine serological tests at three and six months were negative and further tests by Erskine were also negative. There was further evidence—either in the form of previous negative serological tests with former pregnancies or in the history of previous normal pregnancies resulting in healthy babies—to show that the women had not been infected previously. In none of these cases was there anything to suggest an alternative source of infection other than the husband. Such findings, although proving little, are not easily explained and give much food for thought. The possibility of these men having acquired syphilis at the same time as gonorrhoea, the former being modified or masked by penicillin treatment, cannot be dismissed lightly. The mode of transmission of such an infection to the wives is, however, difficult to explain other than by infection from the husbands' semen, in view of the destructive effect of penicillin on treponemata in all superficial lesions, the fact that the wives did not contract gonorrhoea suggests that conception could not have occurred before penicillin treatment for their husbands' gonorrhoea.

#### Case Comments and Histories

The cases listed in the accompanying table are drawn with one exception from cases seen personally at Guy's Hospital Venereal Diseases Department, in addition records from other venereal diseases clinics have been studied and cases described may be considered to represent a selected series out of a total of over 6,000 cases. Some of the records examined showed, however, a high defaulter rate within the first weeks after clinical cure of gonorrhoea.

**Case 1**—This patient was a married man aged 27, who on March 1, 1945, was treated in the Army with 200,000 units of penicillin for acute gonorrhœa. The incubation period of this gonorrhœa is unfortunately not known exactly, but penicillin was administered on the second day after the urethral discharge was seen. The patient responded satisfactorily to treatment, and serological tests for syphilis after three and six months were negative. Almost exactly eleven months after his penicillin treatment he attended at Guy's Hospital and asked for final tests of cure as his wife was pregnant. He stated then and subsequently that he had had no further exposure to infection other than his wife, in whom all tests were negative. Strongly positive Wassermann and Kahn tests were found which were repeated and confirmed. He gave no history suggestive of any skin or other manifestation of the disease. When put on routine anti-syphilitic treatment he showed a mild Herxheimer reaction after his first injection.

**Case 2**—This patient was a single man aged 24 he was not seen personally, and unfortunately no serological tests had been carried out after his treatment for gonorrhœa. On Feb 6, 1947, he was treated for acute gonorrhœa with five injections of 40,000 units of penicillin at two-hourly intervals. He was clinically cured within three days, the incubation period of his gonorrhœa was fourteen days, and he reported for treatment on the fourth day of the disease. On May 3, 1947, he reported to his own doctor with two small 'pimples' on his prepuce, which were treated by the latter with penicillin cream. Two days later he reported at a clinic and was found to have œdema and induration behind the coronal sulcus associated with enlarged inguinal glands. He also had a faint papulomacular syphilitic rash. Dark-ground examination of the penile lesion revealed no treponemata, but a strongly positive Wassermann reaction was discovered.

**Case 3**—This patient was a single man aged 34. On Oct 2, 1944, he reported at Guy's Hospital clinic and was found to be suffering from gonococcal urethritis after exposure to infection six days before. He was treated with sulphonamides, which cleared up his discharge, but he relapsed ten days later. On Oct 12, 1944, he was admitted to hospital and given a total of 130,000 units of penicillin in the form of five two-hourly injections. Within four days he showed clinical cure, which was confirmed by negative serological tests after three and six months. On Oct 16, 1945, he reported with two small 'pimples' on his penis which had been present for one week. He was certain that he had had no further exposure to infection since the previous attack of gonorrhœa. Dark-ground examination of these pimples was

negative, as were the serological reactions. On Oct 31, 1945, penile sores were healed but the Kahn test was weakly positive. On Nov 7, 1945, he had developed a maculo-papular eruption on the trunk—which did not irritate—and some enlarged lymphatic glands. Wassermann and Kahn reactions were strongly positive. Two days later he developed a Jarisch-Herxheimer reaction after the first injections of penicillin and nearsphenamine.

**Case 4**—This patient was a single man aged 27. On July 26, 1947, the patient reported on the first day of urethral discharge, which appeared six days after exposure to infection. He received 250,000 units of penicillin in oil, in one injection. On Sept 16 and Nov 25, 1946, serological tests were negative. On March 13, 1947, he reported with a penile sore which had been present for four days. Dark-ground examination revealed the presence of *Treponemata pallidum*. Serological tests were negative.

**Case 5**—The patient was a single man aged 23. In September, 1946, he was treated at Glasgow for acute gonorrhœa, being given 200,000 units of penicillin in five two-hourly injections. Clinically he was rapidly cured and he defaulted without any further tests. On Feb 18, 1947, he was seen with a large indolent sore in the suprapubic area which had been present for two weeks. He assured us that he had had no further exposure to venereal infection since September, 1946. *Treponemata* were found in the lesion, and his blood showed strongly positive Wassermann and Kahn reactions. He developed a Herxheimer reaction after his first nearsphenamine injection.

**Case 6**—This patient was a married man aged 22. On Nov 23, 1946, he reported with acute gonorrhœa which had been present for two days. He had exposed himself to infection nine days previously. He was treated with 250,000 units of penicillin in oil in one injection. Unfortunately he failed to report for tests after clinical cure. On March 31, 1947, he reported with multiple erosions of the penis and signs on the skin and in the mouth of early secondary syphilis. He admitted exposure to infection one week previous to attending but otherwise none since his previous attendance. Wassermann and Kahn tests were strongly positive, and treponemata were found to be present in the lesions.

**Case 7**—This patient was a single man aged 33. On May 14, 1946, he reported with acute gonorrhœa after exposing himself to infection five days earlier. He was treated with 200,000 units of penicillin in a single injection. His Wassermann reaction was negative. On June 25, 1946, routine Kahn tests

were weakly positive. He failed to attend again before Sept. 3, 1946, owing to a misunderstanding. Wassermann and Kahn reactions were then strongly positive. Careful examination of this patient failed to reveal any signs of syphilis and there was no history to suggest skin manifestations of the disease.

**Case 8**—This patient was a single man aged 22. On Jan. 1, 1946, he reported with gonorrhœa contracted after exposure to infection seven days earlier. He was treated with 200,000 units of penicillin in oil in a single injection. On Jan. 10, serological tests were negative. On Feb. 28, he reported with a small ulcer on the meatus of the urethra. Dark-ground examination revealed the

presence of *Treponema pallidum*. Serological tests were negative.

**Case 9**—This patient was a single man aged 30. On April 8, 1947, he reported with acute gonorrhœa after exposure to infection seven days previously. He was treated with a single injection of 12,000 units of penicillin in oil and sulphathiazole 1 g. every eight hours for four days. By April 13, the gonorrhœa was clinically cured and by April 20, serological tests were negative. On May 6, 1947, he reported with minute nodules on the penis which, although clinically quite unlike a chancre, revealed *Treponemata pallidum* on dark ground examination.

**Case 10**—This patient was a single man aged 29.

TABLE

INCUBATION PERIOD AND METHOD OF MANIFESTATION OF SYPHILIS IN  
SELECTED PERSONALLY OBSERVED CASES

Case No	Time in days		Dosage of penicillin in units	Result of Kahn test	Result of Wassermann test	Result of dark-ground examination	Clinical notes
	from date of exposure to treatment with penicillin	from date of exposure to diagnosis of syphilis					
1	?	c 350	200,000	— + — —	— —	Nil	No physical signs of syphilis
2	18	105	200,000	Nil	++	Negative	Early secondary syphilis
3	16	c 390	130,000	+ — + + + +	Nil ++	Negative	Early secondary syphilis
4	6	239	250,000	Nil	Nil	T pall present	Presented on first attendance with ulcer of penis
5	?	c 150	200,000	+ — + —	+ —	T pall present	Early secondary syphilis
6	9	123	200,000	+ — + —	— —	T pall present	Early secondary syphilis
7	5	46	200,000	+ + + + + +	+ — — — — +	Nil	Latent syphilis — symptomless
8	7	66	200,000	Negative	Negative	T pall present	Urethral chancre
9	4	32	125,000	Negative	Negative	T pall present	No delay in development of chancre after penicillin and sulphonamides
10	35	45	250,000	Negative	Negative	T pall present	Sore on glans penis present at first, disappeared after treatment and later recurring



On Oct 3, 1946, he reported with gonorrhœa which had been present for ten days and which had developed after a 25-day incubation period. He was treated with 250,000 units of penicillin in a single injection. The next day he developed a small superficial sore on his glans penis associated with enlarged inguinal glands. Repeated examinations for treponemata were negative as were serological tests. By Oct 9 the lesions had healed, but on Oct 13 there was recurrence of a sore in the same situation, dark-ground examination revealed treponemata. Wassermann and Kahn reactions were negative.

These cases present some unusual features which strongly suggest that three or six months' surveillance for syphilis is too short a period after the penicillin treatment of gonorrhœa. In some of the cases also the signs of syphilis are slight or even absent, and there may be little or nothing to induce a defaulter to return for advice after the clinical cure of gonorrhœa. An obvious criticism and method of explanation is that the patient's history is unreliable. Many will say that the average venereal patient is unlikely to tell the truth, but, except for the proportion found in any group to whom truth is anathema, I think the correct story usually comes out in the end in a happy and well-run clinic. The cases reported here were reliable men to whom the importance of their story was explained, and there appears to be no reason to doubt that their stories were substantially correct.

Case 1 is possibly an example of the most dangerous type of all, the symptomless development of syphilis in which the progress to late and serious complications may be accelerated by inadequate therapy. Case 2 is included although I never had the opportunity of interviewing him and verifying his story. The extremely long incubation period of Case 3 is surprising in that penicillin in a small dosage was given at a relatively late stage of the gonorrhœa. This patient however, appeared to be a most reliable witness. Case 5 was an unsatisfactory patient in that he ignored tests for cure, he was however, quite emphatic about the absence of further exposure and appeared to be only too willing to make up for his lapse in defaulting without tests. In Case 6, the only intervening exposure could obviously have had no influence on the development of the secondary eruption. Case 7 is interesting in that, like Case 1, syphilis could only be diagnosed on serological tests, all cutaneous manifestations of syphilis appeared to have been suppressed. In a similar manner the primary lesion in Case 9 was clinically quite unlike a chancre, and the ordinary patient and many practitioners would almost certainly have ignored this lesion, and yet dark-ground examination showed a large number

of treponemata present. Case 10 illustrates a phenomenon noted by many previous workers, namely, the appearance and healing of early lesions without any sign of treponemata being present and the subsequent reappearance of the lesion with treponemata demonstrable.

### Statistics of Double Infection

The true double infection of syphilis and gonorrhœa—and in that group only those cases in which the two diseases appear to have been contracted simultaneously are included—has always been a subject of interest to the venereologist because of its surprising rarity. Kemp and Shaw (1936), describing 500 cases of gonorrhœa in males, found that 1.4 per cent subsequently developed syphilis in addition. More recently Lloyd Jones and others (1946b) recorded a series of 250 cases of gonorrhœa of which 4 per cent had double infections, in another series the same authors (1946) record 617 instances of gonorrhœa of which 1.6 per cent became double infections. In both these series of cases syphilis appeared after the penicillin treatment of the gonorrhœa. In a recent series, collected personally at a well known London venereal diseases clinic, of 257 cases of gonorrhœa treated with sulphonamides 2.8 per cent were double infections, of the total number, however just under 10 per cent defaulted after clinical cure of gonorrhœa and before syphilis could be expected to develop.

The statistical reports of the Guy's Hospital Venereal Diseases Department from 1939 to 1947 have been examined, and the period divided into the pre-penicillin and post-penicillin eras. Before penicillin treatment was started, 1,376 gonorrhœa cases were seen, of whom 1.3 per cent had double infections, after penicillin was first used 701 cases of gonorrhœa are recorded, of which 0.9 per cent had double infections. From such figures little reliable information can be drawn, a fair comment would be that the percentage of double infections has fallen slightly in a relatively small series at a time when the general increase in the incidence of syphilis might lead one to expect a rise in this figure. It might be argued that penicillin has some effect in suppressing some of the potential syphilis infections, but it would be unwise to assume this until a considerably larger number had been collected and compared. Records were

studied in other clinics, but unfortunately from reading case records it was not possible in most cases to collect reliable figures as notes did not appear to have been kept with this possibility in mind, and the figures obtained, which varied considerably, were discarded as misleading.

An interesting observation was made in a seamen's hospital clinic in which patients had contracted their infections in places where syphilis is as a rule particularly rife. Out of 300 case records only one double infection was found. It was interesting to note that all had had penicillin, frequently in rather larger doses than is customary—presumably an attempt to guard against relapse at sea while away from medical supervision.

It is unfortunate that venereology, a branch of medicine in which records and statistics have always been regarded as of the greatest importance, has neglected double infections in its statistics. It is only since the advent of penicillin that the significance of this incidence has been appreciated, and yet even in the records compiled in the official venereal records of the United States of America, a country in which statistics have always been accorded their due importance, while syphilis is subdivided into four groups, there is still no statistical record of double infections in 1946. It is obvious that a considerable relative decrease of double infections in the absence of any sudden fall in syphilis rate would at least suggest that for some reason some double infections were being masked or suppressed, especially if the same drop was not noted in sulphonamide-treated cases of gonorrhœa. To decide this point one way or the other, an almost nation wide collection of cases would be required to obtain sufficient numbers to eliminate errors found in smaller series.

It appears from the literature on the subject that there cannot be the slightest doubt that penicillin administered during the incubation period of syphilis, as occurs in the treatment of gonorrhœa, can delay the development of the former disease and may in many ways mask its usual presenting features. Unfortunately there has been no uniformity in the way in which the disease has manifested itself, an analysis of 40 cases reported with details in the literature shows that 22 were diagnosed by demonstration of *Treponema pallidum* in a superficial lesion, 13 were found to have

positive serological tests only, and 5 presented as generalized secondary syphilis. A similar lack of uniformity is seen in the cases described in this paper. It has been shown that it is as a rule impossible to demonstrate treponemata in lesions of the skin or mucous membrane within a few hours of systemic penicillin treatment, and as might be expected, a large number of the cases described presented with lesions clinically suggestive of primary chancres in which, however, no organisms could be demonstrated. After a short period these lesions healed, but subsequently these either recurred and treponemata were usually found in the recurrent lesion, or there was no further localized lesion but the patient developed all the signs and symptoms of secondary syphilis, in some cases, however, the diagnosis was made on a positive serological test only, without any accompanying signs or symptoms.

If the ultimate development of syphilis is obvious enough to make the patient seek further advice, no very great harm may have been done, but it is alarming to note, after inspecting some 6,000 case records, the large number of defaulters after rapid clinical cure of gonorrhœa with penicillin. The venereal habitué now finds that gonorrhœa is cured more rapidly and satisfactorily than a common cold, and, with this realization, virtue loses yet another inducement and promiscuity becomes more rife, penicillin soon restores him to his usual health and he readily forgets the warning he has received about routine tests at three and six months intervals. The manifestation of secondary syphilis, when modified by previous penicillin treatment, may also be trivial and transient and escape the notice of an unobservant patient or even his medical practitioner.

The few cases quoted in this paper are valuable in that they provide highly suggestive evidence that the *Treponema pallidum* is behaving under the influence of penicillin in a way not yet fully understood. The evidence given of the fall in incidence of double infections at a time when syphilis has been on the increase for a few years is significant but not conclusive with such a small series. However after discussing this incidence with venereologists over the last few months I am left with the impression that all, without exception, have been surprised at what appears in their

opinion, to be an unexpected fall in this incidence over the last three years

Possibly in those cases failing to develop a primary lesion or even secondary generalized signs, we may be seeing an artificial syphilis d'emblee. Morgan's experiments with rabbits in which he showed that the inoculation of less than 30,000 treponemata produced no local lesion but did in due course cause a systemic syphilitic infection, as was shown by positive serological tests, suggest that this is a possibility. The effect of penicillin may in some cases attenuate the original inoculum to such an extent as to interfere with the local growth of treponemata. It is known, however, that treponemata in the skin are more vulnerable to treatment than those that are disseminated and lie sheltering in some lymph node. The similarity between this hypothetical case and Morgan's experimental rabbit is obvious.

The importance of the skin as an organ of immunity has always been recognized in syphilis. Urbach (1946) in his book on allergy points out that in fevers and diseases like syphilis and tuberculosis, where the skin reactions are severe, visceral manifestations are less marked. Brown and Pearce (1921) formulated their law of inverse proportion on similar findings.

Bloch (1923) (quoted by Urbach) managed to transfer specific hypersensitivity in Thiersch grafts, demonstrating the existence of antibodies in the epidermis. Haxthausen (1939) (quoted by Urbach) showed that intracutaneous injections of foreign serum produce a greater reaction in the skin than intravenous injections, suggesting that the bulk of the effective cutaneous antibodies are formed in the skin itself. Matsumoto (1936) (quoted by Urbach) demonstrated the greater effect of giving vaccines intradermally, a fact of great importance to all dermatologists. All these findings suggest that a brisk primary or secondary reaction in syphilis is, from the ultimate prognostic point of view, an excellent sign. Yet there is evidence available already that we are suppressing or modifying this reaction with penicillin given during the development of the disease. Even provided all such cases are ultimately correctly diagnosed and treated, there must be some doubt in our minds as to whether their ultimate prognosis is as good as that of cases of uncomplicated chancres treated in the orthodox manner.

### The Skin and Immunity

At the 1947 Annual Conference of the British Association of Dermatology and Syphilology at Leeds, the main discussion was on the effect of calciferol on tuberculous disease of the skin. Results reported over a relatively short period of time give a very encouraging picture for the future of the patient suffering from lupus vulgaris. Several workers were, however, distinctly disturbed to note that in some cases, as the skin condition was improving, tuberculous lesions developed or flared up in the lungs. Although no statistics were available the impression formed was that such a complication was becoming not uncommon and was certainly a great deal commoner than previously when lupus, although sometimes controlled, could not be cured. An analogy was drawn at this meeting between this phenomenon and syphilis with special reference to Bruusgaard's findings, showing the great rarity of tertiary skin lesions combined with neurosyphilis. Lane's cases of syphilis d'emblee described in this paper furthermore suggest that a large well developed chancre may be a good prognostic sign.

Stokes and others (1934) in their survey of the results of treated syphilis compared their figures with Bruusgaard's findings in Boeck's cases. The most striking difference is in their relative late skin, mucosal, and bone infection figures, in the 3 to 10 year group Stokes reported 1.2 per cent in this form, while Bruusgaard reported 31.7 per cent and yet the latter's final figures for general paralysis of the insane in untreated cases was estimated finally at 0.6 per cent. That the skin has some influence on immunity is suggested by these figures alone. The exact form of this immunity is not known, and the question has been discussed in this paper. The passing of the primary and secondary stage of syphilis is heralded by massive destruction of treponemata in the superficial lesions. Exactly how this comes about is again unfortunately not known, but it is known from clinical experience that the skin and mucous membrane are the only organs of the body, with the possible exception of bone, liver, and the eye, in which spontaneous healing of a syphilitic lesion normally takes place. It therefore would appear to be the height of folly to deprive this organ of its chance of producing some immunity against the disease, unless the most rigorous treatment

is subsequently to be given to eradicate the treponema from the body

### Eliminating Risk of Masked or Modified Syphilis

In view of the cases described in this paper and the previously recorded facts and hypotheses, it would appear that the case for dissociating penicillin from any risk of masking or modifying syphilis, even after the six-month period of surveillance that is now generally accepted, is not proven. In spite of the relative rarity of double infections, the very serious potential results of an undetected masked syphilis necessitate a careful examination of this subject, it is too early yet to assume confidently that all such cases showing no signs of syphilis are entirely free from infection. Chesney's account, already described earlier in this paper, of experimentally infected rabbits and monkeys in whom treponemata, capable of reinfecting another animal, were found in lymph nodes without any other signs of syphilis, even in the form of a positive serological test, must be remembered.

Certain suggestions therefore are made with a view to eliminating this risk as far as possible.

1 Bigger (1944) showed that, in vitro, penicillin and sulphathiazole showed a synergic reaction, having an enhanced combined effect on *Streptococcus haemolyticus* and *Staphylococcus aureus*. It is suggested, therefore, that a combined therapeutic course of penicillin and sulphathiazole be given, so that the dose of the former may be dropped to 125,000 units, this routine has been in use at Guy's Hospital clinic for some months and has proved very satisfactory. One case of double infection in which the gonorrhoea was treated in this manner is quoted in my series as showing no delay in the development of syphilis. Cronin, whose work has already been described, claims that with 100,000 units of penicillin there is little or no delay in the development of syphilis. My figures and those of published cases suggest as might be expected, that doses of 200,000 units and more have an appreciable delaying or masking effect.

2. A patient about to receive penicillin for gonorrhoea should always have a serological test for syphilis performed before treatment, he should also be carefully examined for any evidence of early chancres not noted by the patient.

3 Records of true double infections should be kept. Only when the percentage of this association in a very large series of cases is known is this of any value, a substantial fall in this percentage during the routine six-months period of surveillance at present generally accepted, as compared with the days before penicillin was used in treatment, would suggest that syphilis is possibly being suppressed or masked.

4 No pregnant woman should be given penicillin for gonorrhoea except either immediately before full term or after two unsuccessful courses of sulphonamides by which time a chancre might be expected in most cases to be visible. Batchelor (1946) originally made this suggestion and the possibility of masking congenital syphilis in the baby is, in our present state of knowledge, very likely.

5 In view of the widespread use of penicillin in present times, all practitioners should appreciate that systemic penicillin rarely gives rise to any skin eruptions, except occasionally urticaria, or rises in temperature and rigors and they should regard the latter as potentially a Jarisch-Herxheimer reaction and the former as possibly a generalized cutaneous form of syphilis brought on by the penicillin injection. Cronin (1946) describes five cases that might well have occurred in general practice where the practitioner, unless fully acquainted with the facts described above and their significance, would very probably have missed the true diagnosis and dismissed an evanescent macular rash as a toxic erythema, unless previously warned of the possible complications of penicillin treatment.

6 All patients after having penicillin treatment for gonorrhoea should be warned of the dangers of not attending for further tests as instructed, or of not reporting any abnormality. While there are obvious psychological disadvantages in this, as Cronin (1947) points out, I think the average patient will appreciate the reason after explanation and may well have more confidence in his treatment.

7 Serological tests should be carried out for at least one year after penicillin treatment of gonorrhoea. Psychologically this is bad for a certain type of patient, but the wise venereologist should have little difficulty in reassuring such patients yet at the same time impressing on them the importance of attending for such tests. At the time a physical examination

should be made, too in case a superficial lesion has developed without affecting a serological reaction

8 On the evidence given by Earle Moore at a recent meeting at the Royal Society of Medicine, it is considered advisable to avoid the use of penicillin "G" in the treatment of gonorrhœa, because this particular form of penicillin has a more marked anti-syphilitic effect than other forms and might tend to mask the disease to a greater extent

### Conclusion

The full answer to this problem may not be written until ten or even twenty years hence. I have endeavoured to draw attention to what I consider is a future possibility—a sudden increase in the gravity of syphilis which, while being almost unnoticed in the early stages of its onset, once again becomes the fatal and destructive disease that killed, after mentally maiming, such well known figures in the past as Guy de Maupassant and many others. The best and almost the only treatment for neurosyphilis is prevention. We must avoid taking a possible backward step in our therapeutic progress in the study of venereal disease.

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# THE PROBLEM OF DEFAULT IN A VENEREAL DISEASES CLINIC

## A MEDICO-SOCIAL ANALYSIS OF 381 WOMEN PATIENTS

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In 1943 the Tyneside Experimental Scheme was introduced as a measure to combat the rising incidence of venereal disease, and it took into consideration the fact that something more than medical treatment was necessary. The area covered by this scheme includes the County of Northumberland, the Tyneside area of Durham County, and the County Boroughs of Newcastle, Gateshead, Tynemouth and South Shields. Serving the greater part of this area is the Joint Committee's Clinic, situated in the grounds of the Newcastle General Hospital and the social department of the experimental scheme operates from there. While the scheme was primarily designed to persuade all women attending ante-natal clinics to have an ante-natal Wassermann examination and also to locate contacts of venereal disease through interrogation of infected patients, it soon became obvious that default from treatment was an equally serious and important problem. This paper is an attempt to analyse the reasons for default and the efforts made to persuade defaulters to resume treatment.

### Scope of the Inquiry

Three hundred and eighty-one women in default of treatment at the end of 1945 or during the first half of 1946 were selected for study. The group included 33 with congenital syphilis, and these are separately considered as their problems were different.

### Acquired Infection

There were 48 single women, 230 married, 48 separated, 20 widowed and 2 divorced (Tables I, II, and III).

Default from early treatment implies that the patient had not completed a full course of penicillin together with a course of arsenic and bismuth or alternatively where penicillin was not employed at least two courses of arsenic and bismuth. A course of arsenic and bismuth consisted of 10 intravenous injections of a 914 preparation and the same number of bismuth metal injections given intramuscularly usually at weekly intervals. Default during early surveillance means that the patient had ceased attending for observation before the end of the first year after the completion of syphilis therapy. Patients with gonorrhoea who defaulted during early surveillance ceased to co-operate some time between three weeks after the administration of penicillin and six months after the date of exposure to infection.

The outstanding feature in Table III is the large number (76 per cent.) of women suffering from early syphilis who defaulted in the early

TABLE I  
AGES OF THE PATIENTS AND DIAGNOSIS (EXCLUDING CONGENITAL SYPHILITIC PATIENTS)

Age	*Early syphilis	†Latent syphilis	‡Late syphilis	Gonorrhoea	Dual infections	Total
—21	15	—	—	10	4	29
22—30	103	3	1	52	23	182
31—40	42	19	7	21	10	99
40+	12	8	9	7	2	38
Total	172	30	17	90	39	348

\*Early syphilis = Patients with primary or secondary lesions and those who had asymptomatic infections of less than 4 years' duration.

†Latent syphilis = Asymptomatic patients where duration of infection exceeded 4 years.

‡Late syphilis = Clinical active infection which had reached tertiary stage or later.

TABLE II  
SOURCES OF INFECTION

Source	Number
Single women who were infected	48
Marital infection	51
Extra-marital infection	105
Infected before marriage	32
Infected subsequently to termination of marriage	16
Source not known (married women)	96
Total	348

phase of treatment. Including those suffering from dual infections, 90.7 per cent of syphilitic women defaulted during treatment, and the corresponding figure for those infected with gonorrhœa was 77 per cent. Obviously such a state of affairs demanded the closest attention from the medico-social unit.

**Follow-up of Default**—The period of grace was determined by the nature of the disease; the amount of treatment received, and the mode of therapy employed at the time of default. No more than twenty-four hours were allowed to elapse before action was taken where a patient was receiving penicillin treatment, equally urgent was the infected female fairly advanced in pregnancy, or the highly contagious syphilitic who perhaps had attended once or twice at the most. Three or four weeks were allowed in a case under surveillance before a letter was despatched. Domiciliary visiting was the method of choice in urgent cases such as those already cited or where family circumstances or illness prevented a patient from attending regularly. It cannot be too strongly emphasized that the speed with which default was detected and followed up was the keynote to success in preventing complete default.

The amount of work required to persuade defaulters to return varied considerably in the group of 348 under review. The minimum was one letter and the maximum 14 letters and 6 visits all to one person, the average was 9.5 efforts per patient and the total efforts amounted to 1,460 letters and 1,860 domiciliary visits. 804 of the latter proved to be ineffective since the patients were not seen at home. The ratio of ineffective to effective visits was 4 to 5, and when planning work allowance had to be made for these relatively wasteful visits. In densely populated areas this was not so extravagant of time, as the visitor could call at other homes in the vicinity, but in the country districts the social worker relying on public transport could spend half a day or more on one ineffective visit. The benefits of domiciliary visiting were not restricted

to the effect it had on persuading patients to return. Most patients were inclined to talk more freely in the familiar surroundings of their own homes, and the social worker was often able to gain a more reliable and complete picture of the patient's circumstances and the true difficulty in the way of her attendance. If this was a practical one it could usually be disposed of with the help of the almoner. The greatest care and tact were used by the visitors, and it was found that trouble was hardly ever caused by a visit, whereas letters, although marked "strictly confidential," were sometimes opened by others.

**The Results of Social Efforts**—The records of the 348 defaulters have been analysed and their default classified under the following terms:

Initial default—defaulted once and re-attended	16
Initial and complete default—defaulted once and failed to re-attend	70
Intermediate default—defaulted twice and re-attended both times	89
Persistent default—defaulted at least three times and re-attended each time	51
Persistent and complete default—defaulted twice or more and failed to re-attend	122

In the "initial and complete" section (70 women) were included 62 who defaulted shortly after their first attendance at the clinic. It will be realized that in the "persistent" section many had defaulted repeatedly and had received frequent visits and letters after each default.

From Table IV it will be noted that 55 per cent of these 348 women could not be persuaded to return, and that a further 4.5 per cent are defaulting—once more.

TABLE III  
CLASSIFICATION ACCORDING TO THE NATURE OF INFECTION AND THE STAGE IN WHICH DEFAULT OCCURRED

Type of infection	No of patients	Defaulted during treatment		De-faulted during surveillance
		Early	Late	
Early syphilis	172	126	27	19
Latent syphilis	30	24	4	2
Late syphilis	17	12	4	1
Gonorrhœa	90	69		21
Dual Infections { Early syphilis	36	33	1	2
{ Latent syphilis	3	3	—	—
{ Gonorrhœa	39	31	—	8

TABLE IV  
THE RESPONSE TO SOCIAL EFFORTS

Results	Early syphilis	Latent syphilis	Late syphilis	Gonorrhœa	Dull infection	Total
Re-attended	63	12	9	33	13	130
Re-attended but defaulting periodically	12	—	2	2	—	16
Transferred	5	—	1	2	2	10
Complete default	92	18	5	53	24	192
Total	172	30	17	90	39	348

**Default during Pregnancy**—Of 8 patients who defaulted from anti-gonorrhœal treatment during pregnancy, only 2 could be persuaded to re-attend until cured

Seventy-seven pregnant syphilitic women presented a much more serious problem, since inadequate anti-syphilitic treatment was liable to produce unfavourable results in the health of both mother and unborn offspring. In the course of assisting those defaulters in every way, it was ascertained that failure to co-operate was not attributable to illness or difficulties associated with pregnancy. Of the 14 who before their default had received adequate treatment, the outcome of pregnancy was known in 10 instances, but of the 63 whose treatment was inadequate the outcome was known only in 15 patients. Although those numbers were too small to justify any con-

clusions, they provided an interesting comparison. In the adequately-treated group 2 infants died in the first year of life but 8 others were healthy. The inadequately-treated section showed a more unfavourable result, since only 3 children were healthy, 2 had congenital syphilis, 5 died in the first year of life, 1 infant was transferred, and other pregnancies terminated in 2 abortions and 2 stillbirths.

Two hundred and thirty-two of these defaulters had a history of previous pregnancies and these were investigated and the results compared with a control group.

Only by careful autopsy examination could syphilis be excluded in the foetus when the reasons for the unfavourable outcome of 14 pregnancies were considered. In the stillbirth and neonatal death rates syphilis usually plays an important part, a factor which was not fully appreciated as gross external evidence of the disease might not have existed.

It would be reasonable to assume that these women, remembering the unfortunate results of previous pregnancies, would co-operate better when again pregnant, especially when syphilis was known or suspected to have been responsible for those results. A number did come for anti-syphilitic treatment, but it required intensive social work to ensure regular attendance. Others defeated the most assiduous efforts of the social workers, the extent of which can be gauged from the fact that 138 letters and 181 domiciliary visits (including 65 ineffective) resulted in the co-operation of only 15 out of those 30 women. The worst

TABLE V

COMPARISON OF RESULTS OF PREVIOUS PREGNANCIES IN (a) 232 DEFAULTERS UNDER REVIEW AND (b) CONTROL SERIES

	No of women	Total pregnancies	Disease	Outcome of pregnancy					
				Abortion	Still birth	Alive and well	Neonatal death	Died in 1st year of life	Congenital syphilis
Defaulters under review	179	474	Syphilis	46 (8.9%)	19 (3.7%)	373* (72.3%)	16 (3.1%)	47 (9.1%)	15 (2.9%)
	53	129	Gonorrhœa	18 (12%)	2 (1.4%)	111 (74%)	2 (1.4%)	17 (11.2%)	—
Control series	232	603	Non V D	27 (4.5%)	14 (2.3%)	514 (85.3%)	15 (2.5%)	32 (5.4%)	—

\* These children are presumed to be free from syphilis inasmuch as 76% of them were not brought to this department for examination.



offenders were those suffering from early syphilis, since only 33 per cent responded in spite of 102 letters and 124 visits. They showed the reluctance and lack of responsibility characteristic of all those suffering from early syphilis in this investigation.

### Congenital Syphilis

Thirty-three patients with congenital syphilis were studied separately, because although their numbers are small their default may be due to other factors from those which underlie the default of patients who have acquired venereal disease. There were 21 with active lesions which would cause discomfort or pain (14 with interstitial keratitis, 4 with periostitis, 2 with neurosyphilis, and 1 with secondary manifestations). Co-operation only became a problem when these symptoms subsided.

The ages of the patients were important, as the responsibility for their default could not be laid upon those who were children, of whom some were too young to travel alone and none of whom, if not more than 16 years old, could be expected to understand the necessity for treatment. In Table VI the ages given are those of the patients at the time of their default, since this is the problem under investigation. At the time of their first attendance, 9 of the 21 with active lesions were below 16 years, but only 4 were still in this age group when they ceased attending. Of the remaining 12 patients who were without active symptoms, 4 were less than 16 years when they originally attended but only one was under 16 at the time of default. It is interesting to note that 18.5 years was the average age at which patients with interstitial keratitis first reported.

In congenital syphilis, as in all other types of

syphilis, it was usually the lack of pain or discomfort and of obvious external symptoms that was the chief cause of default. Even patients who were suffering acutely when they first came and who in a short time gained relief through their treatment quickly forgot the warning and did not continue to attend.

Six stillbirths and 18 neonatal deaths were recorded in the previous pregnancy histories of 23 congenital syphilitics, all of whom had received little or no treatment.

The social work on behalf of these patients resulted in 19 re-attending, but one of these has recently defaulted again and the remaining 14 have completely defaulted. The reasons given for default were

Other illness of the patient, or pregnancy	4
Fear of being found out	2
Fear of treatment	2
Discouragement at prospect of prolonged treatment	5
Ignorance of the seriousness of the disease	11
Objections by family	3
Family trouble	4
Miscellaneous reasons	2
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The social problems of patients with congenital syphilis are complex, often involving other members of the family to an even greater extent than in acquired venereal disease. For parents of children suffering from congenital syphilis there is bound to be some difficulty in giving an acceptable explanation for their need to attend when the children grow old enough to appreciate their surroundings. Unless care is exercised by the clinic staff the curiosity of the child may cause the parents grave embarrassment. It is a difficulty which can be

TABLE VI  
CONGENITAL SYPHILIS—SOCIAL EFFORTS IN RELATION TO DEFAULT

Age	Clinical condition		Default during				Social efforts		
			Treatment		Surveillance		Letters	Visits	
	Active	Inactive	Early	Late	Early	Late		Effectual	Ineffectual
—16	0	5	4	1	—	—	18	15	16
17+	0	28	17	4	5	2	110	97	36

overcome, and the practice of not allowing children to wait long among other patients prevents some awkward questions, but parents may be so afraid of these questions arising that they will not take any risk and may stop coming. The default of two children could not be excused on these grounds as they were under 3 years old. The ages of the other 3 children were 5, 10, and 13 years.

Among 28 patients over 16 years of age 23 were married and 10 of these marriages had taken place after the patients had reported at the clinic. Some had not disclosed to their husbands the fact that they were suffering from congenital syphilis and were afraid that they might be found out. Until there is a more enlightened public opinion it seems that many people will be doomed to carry this burden of fear through life.

It was hardly surprising that women who had attended for years, perhaps since early childhood, had become discouraged. It did, however, seem strange when other members of the family objected to these patients attending for treatment, sometimes it was the husband who was afraid of scandal sometimes parents or brothers and sisters of the patient were afraid that they might be implicated. Most women with congenital syphilis had a very generous attitude to their parents but some felt a grudge against them or more vaguely, against life itself for its injustice.

Whilst two of these women had histories of sexual contact, there was no evidence of serious promiscuity in the whole group and none of them had any illegitimate children.

#### Crude and Corrected Defaulter Rates

The crude defaulter rate is the percentage of patients who default during the year, and the corrected defaulter rate is determined by deducting from the total number of defaulters those who re-attend through the efforts of the social department or are known to have attended clinics elsewhere. During 1946 the use of penicillin therapy on a large scale increased the defaulter rate in men and women patients whether they were attending with syphilis or gonorrhœa.

With the exception of men with gonorrhœa all patients treated with penicillin had higher corrected defaulter rates than those who received treatment in other forms.

The marked difference between crude and

TABLE VII  
CRUDE AND CORRECTED DEFAULTER RATES OF ALL PATIENTS SUBJECTED TO PENICILLIN AND OTHER FORMS OF THERAPY DURING 1946

Disease	Sex	Penicillin treated			All forms of therapy
		Crude	Corrected	Corrected rate	
Syphilis	Male*	26.6	8.7	4.0	
	Female	44.6	11.2	5.4	
Gonorrhœa	Male	39.6	10.5	11.1	
	Female	48.1	11.4	6.9	

\* The efforts (1023) of the male social worker resulted in 625 men defaulters returning to complete treatment.

corrected rates could be chiefly attributed to efficient social work. The results of this one aspect of medico social work clearly support Osler's contention that such a unit is essential in a venereal diseases department.

Both crude and corrected defaulter rates revealed that men co-operated better than women patients and if they defaulted they responded more readily to the efforts made to bring them back. For obvious reasons men were especially susceptible to letters, even non-committal ones. If however they ignored the letter the male social worker visited their homes. Fully 80 per cent of those who were persuaded to return continued to attend until cured. The rapid disappearance of external symptoms in gonorrhœa and in early syphilis undoubtedly encouraged default, and this reason applied equally to men and women. The persistent active manifestations of late syphilis were usually strong enough incentives to attend for treatment and they discouraged default among these patients.

Women with secondary syphilis were notorious defaulters irrespective of the kind of therapy employed. This has become particularly important since the incidence of contagious syphilis among women has increased ten times in the last nine years in Tyneside. Those with primary syphilis usually came to the clinic as the contacts of their husbands who had inadvertently exposed them.

to infection, and they adopted a more reasonable attitude all through the course of treatment. The patient who had already revealed the secondary stage of syphilis when she attended for the first time had waited until obvious symptoms were present. She may have unwisely refused to come for observation at her husband's request, or he may not have revealed to her the need to come, though he was interviewed repeatedly until she did report, but more likely her infection had been acquired extra-maritally and she might not have known that her consort was infected. These women were often promiscuous, and it was difficult to convince them of the necessity to attend regularly for a long period.

The corrected defaulter rates for female syphilis and gonorrhœa contrasted favourably with the high percentage (55 per cent) of complete default among 348 women reviewed in this paper. It is clear that the latter represents the hard core of defaulters among all women attending this department with venereal infection.

### Discussion

It was the need for consistent attendance during the periods of treatment and surveillance, especially the former, that constituted the difficulty for venereal diseases patients. There was almost always present in the minds of patients a sense of guilt or injury which had a strong and adverse influence on their attendances. After the initial stages of treatment in early contagious venereal disease they usually felt quite well and may not have shown any outward symptoms so that they found it difficult to appreciate the importance of persevering with treatment and even more difficult to understand that they should have continued to come until the tests of cure were completed. Default especially in gonorrhœal patients treated with penicillin, might occur immediately after the first or second attendance for treatment, at the very end of the period of surveillance, or at any of the intermediate stages.

**Reasons for Default**—There were many ingenious and varied excuses made by patients to explain their default, some were obviously irrelevant, some false, and others, although true, were only of temporary influence, for example, minor illness or bad weather. The

excuses given by defaulters, the visitors' reports, and the facts known about the home circumstances have been carefully considered and an attempt made to deduce the real reasons, a list of which is appended.

<i>No address</i>	
Moved—unable to locate	26
No fixed abode or false address given	4
<i>Patient's health</i>	
Temporary illness	10
Chronic illness	9
Pregnancy	11
Unfavourable reaction after treatment	6
<i>Fear</i>	
Of being found out	35
Of being reprimanded	3
Of treatment	2
<i>Non co-operation</i>	
Irresponsible (some with low-grade intelligence)	111
Ignorance of the seriousness of the disease	50
Refused treatment	9
Temporary absence from home	6
Discouraged	3
Resented being infected	2
<i>Domestic problems</i>	
Trouble in family	19
Illness of relatives	10
Objections or opposition from relatives	4
Home duties	11
<i>Clinic attendance problems</i>	
Hours of work	12
Gossip in the waiting room	1
Transport, not easily accessible	4
	<hr/> 348 <hr/>

**Address**—A false address was seldom given deliberately (only two examples were found in this investigation) but patients frequently failed to report a change of address and they left their former homes without arranging for correspondence to be forwarded. This may have been intentional, to avoid creditors or police, but more often it was just an oversight. Patients who had no fixed abode were quickly and irretrievably lost.

**Health**—Temporary illness or pregnancy was frequently the original cause of failure to attend, and unhappily they sometimes set up a habit which it was difficult to change. Irregular attendance and finally complete default in some cases was due to chronic ill health. If

it was possible for sick patients to attend without danger to their health, transport was arranged for them, but even so some could not make the necessary effort to come. Prolonged ill health accounted for only about 2.6 per cent of the default.

*Fear*—A few of the defaulters claimed to be afraid of treatment, and some said they had not re-attended for fear of being reprimanded, but much more important, both in numbers and in effect, was the dread of being found out. The fear applied to women who were infected by their husbands, and of course still more to those who acquired the infection outside of marriage. For the latter, disclosure might have meant divorce or, for the single woman, the risk of being turned out of her home. When a wife was infected by her husband she usually forgave him, but sometimes discord occurred later if relatives discovered what had happened and interfered between them.

Patients found it difficult to account to curious relatives for having to be absent from home at frequent and regular intervals.

*Non-co-operation*—This was undoubtedly the core of the default problem. The irresponsibility of the woman who had become infected through her own immoral conduct was shown in her attitude to treatment, she would not attend regularly, was impervious to letters and visits, would give half a dozen contradictory excuses, and lacked either the intelligence to understand the serious implications of the disease or the will power to make any consistent effort to come regularly. Of all default, 44 per cent. was believed to be due to irresponsibility. Included in this group were 36 women who, knowing they were infected, continued to have intercourse and would not attend for treatment. Before defaulters were given up the grave risks of untreated or inadequately-treated venereal disease were explained to them, some appeared unable to understand, and some refused to be convinced.

*Domestic problems*—Genuine family troubles, illness, or serious opposition from parents or husbands accounted for 12 per cent of the default. The patient sometimes refused to permit the almoner to see the family and try to adjust her difficulty, even though they knew that she was coming for treatment, for fear of raising the subject again. Most

careful explanation of the importance of treatment did not always outweigh the immediate unhappiness they expected would result from insistence upon attending.

*Clinic attendance problems*—A very small number, only 4 in the present inquiry, lived in such inaccessible places that transport was a real problem. They lived 50 miles or more away and attendance meant being absent from home for the greater part of a day. Despite the number of sessions held daily some found it difficult to get away from work; these were usually people engaged in domestic work in hotels and institutions. Much was said about the gossip in waiting rooms and it is unfortunately true that patients with late syphilis or congenital syphilis who have attended a long time will discourage others. Very occasionally women of doubtful character talked in an unseemly way in front of respectable women. More often the dislike of waiting-room gossip was explained by the dread of being seen there by someone who knew them and might talk about them at home.

*Immoral Conduct*—The high extra-marital rate of infection (Table II) was due to the fact that many women were infected during the prolonged absence of their husbands who were serving in the Forces, and allowance must be made for additional temptations to which women are subjected in these circumstances, but a large number were either living a normal married life with their husbands at home or were seeing them at fairly frequent intervals. Twenty had a previous history of venereal disease before they had acquired their current infection. 14 had been infected once, 4 on two occasions, 1 thrice, and 1 on four occasions. Further evidence of their immoral or promiscuous conduct was revealed by the fact that 41 had given birth to illegitimate children. Sixty-six women had histories of promiscuity and 22 were known to be prostitutes.

Drink, often the inseparable companion of venereal disease, was observed to be a habit of many, and 41 women were regular or heavy drinkers. Police records were not consulted but it was known that 7 of these defaulters had been convicted in the courts for larceny, disorderly conduct, or child neglect.

The majority of women had very limited interests and as a refuge from boredom or loneliness sought pleasure in the streets or

public houses and sexual immorality was accepted by them as the price of a "good time" or as part of it. The inescapable deduction from these various facts is that there was conclusive evidence of a grave relaxation of moral control in these women.

**Dual and Subsequent Infections**—Although 39 patients (9.7 per cent) had dual infections of syphilis and gonorrhoea when first examined in this clinic, there was no evidence to prove whether the diseases were concomitantly acquired or not. In this section there were 15 promiscuous women and another 5 known to be prostitutes, and it may well be that the two infections were acquired separately by them. Analyses made periodically in this clinic have shown that the incidence of dual infections at the time of the initial visit varies from 2.5 per cent to 4 per cent. The relatively high figure (9.7 per cent) in this series suggests an irresponsibility of conduct which exposed the person to the risk of infection in the first place and led to an unco-operative attitude later when treatment for venereal disease had become necessary.

Dual infections must be distinguished from reinfection, which was not uncommon amongst patients who were suffering from gonorrhoea when they first attended. Thirty-one women were reinfected with gonorrhoea. Reinfection occurred in 21 whilst they were still under treatment for the initial attack, in one during surveillance, and in 9 during the period of their default. Undoubtedly the majority of patients with venereal disease acquired their infections from persons who at the time had not been treated for that attack. On the other hand, a patient under treatment or surveillance, having acquired a new infection, might have infected others before reporting again for treatment.

**The Complete Defaulter**—Forty-eight per cent of complete defaulters were suffering from early syphilis and had received totally inadequate treatment. This figure compares unfavourably with the results of two similar investigations carried out in this department amongst women suffering from contagious syphilis, where 9 per cent of 242 and 13 per cent of 372 defaulted completely. It must be remembered, however, that the present series was selected in order to study the problem of default and included many patients carried forward from the previous year.

## Conclusions

It is not enough to treat patients for contagious venereal disease, every effort must be made to find the persons responsible for the infection and persuade them to attend for treatment. This may entail a considerable amount of work for the medico-social department, which is also responsible for checking and following-up default. The busy general practitioner does not have the time or the facilities at his disposal to follow-up default or to locate the source of infection.

The complete defaulter suffering from contagious venereal disease, especially early syphilis, and the pregnant woman with syphilis require serious consideration. Only compulsory legislation will bring back these careless and irresponsible people, and the time for it is long overdue, but compulsory legislation could be supported only if the following conditions were fulfilled.

(a) The diagnosis and treatment of venereal disease should be the responsibility of competent venereologists who would work in clinics with efficient medico-social departments maintaining close liaison with welfare departments and local authorities.

(b) Adequate buildings situated preferably in polyclinics.

(c) Efficient laboratory facilities.

(d) Legal action should be taken only after reasonable efforts have been made by competent social workers to persuade patients to attend for treatment and when, after attempts to secure co-operation by voluntary means have failed, they have been warned that prosecution will follow.

(e) Propaganda. At present it is not really effective as paper propaganda does not reach, or if reaching does not influence, the sexually promiscuous. Instruction in sex in schools and youth clubs is a more hopeful line of approach. Propaganda needs to be sustained and personal and should aim not only at preventing infection with venereal disease but at inculcating higher moral standards of conduct.

## Summary

Three hundred and eighty-one women suffering from venereal disease defaulted either during treatment or surveillance. No fewer than 172 of these were patients with early

syphilis, 73 per cent of whom had received very little treatment

The functions of a medico-social unit in a venereal diseases department are discussed, and efforts to persuade defaulters to co-operate are recorded. In spite of these efforts 55 per cent proved to be completely unco-operative.

The crude and corrected defaulter rates for syphilis and gonorrhœa are discussed and illustrated.

Various reasons for default are mentioned,

but irresponsibility is undoubtedly the chief reason. It would appear that subject to certain qualifications additional legislative measures are clearly necessary to cope with the irresponsible defaulter suffering from transmissible venereal infection.

The help and co-operation of the medico-social staff of the clinic are gratefully acknowledged. For the investigation of the control group in Table V we are indebted to Mr. Linton Smith, Surgeon in charge, Department of Obstetrics and Gynaecology, Newcastle General Hospital.

## CORRESPONDENCE

### ARSENICAL ENCEPHALOPATHY

Sir—I am indebted to Col. Harrison for drawing my attention to a misquotation which appeared in my recent article on arsenical encephalopathy. I would like to take this opportunity although inadvertently belated of apologizing for the error. This was due to the fact that in the great welter of international literature from which I had to excerpt views, I had not been able to obtain access to the original texts in many cases and had to rely on the statements made by later annotators. This instance provides an excellent example of the oft repeated dictum,

Always verify your references!

I am, etc.

E. E. PREBBLE

Canterbury

## ABSTRACTS

(This section of the JOURNAL is published in collaboration with the two abstracting journals, *Abstracts of World Medicine*, and *Abstracts of World Surgery, Obstetrics, and Gynecology*, published by the British Medical Association. The abstracts are divided into the following sections: syphilis, (general, therapeutic pathology), gonorrhœa (general, therapeutic, pathology), other venereal disease conditions, public health. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.)

### SYPHILIS (Therapeutic)

Reactions to Twenty-day Intensive Therapy with Mapharsen and Bismuth for Syphilis with a Note on the Use of Bal in their Management. CORMIA, F E U, and BLAUNER, S G (1947) *Amer J Syph*, 31, 135

Five hundred patients, of whom 185 had serum-negative and 164 serum-positive primary syphilis, 89 secondary syphilis, 60 latent syphilis, and 2 asymptomatic neurosyphilis, were treated by the 20-day intensive schedule with 1 mg "mapharsen" per kilo body weight daily (maximum daily 75 mg) and 0.2 g of bismuth subsalicylate every 3 days to a total of eight injections.

In the first 300 patients the blood count was taken and the non-protein nitrogen was estimated on admission and weekly thereafter. White-cell counts were taken in the middle of each week, the icterus index was determined, the urine examined, and the Rumpel-Leede tourniquet test performed every 3 days. Temperature records gave the most valuable evidence of toxicity. In the remainder of the patients the number of white cells and the non-protein nitrogen were estimated on admission and on discharge, and the icterus index was determined and the urine examined weekly.

Treatment of 476 patients was complete and of 24 incomplete. Of these last, 7 had cerebral irritation, 6 jaundice, 3 toxic erythema, 3 agranulocytosis, 2 severe fever, 2 hæmorrhagic encephalitis, and 1 persistent albuminuria. Reactions in 190 (37.6%) were sufficiently severe to cause modification of the schedule, of these, 125 had fever, 33 toxic erythema, 14 cerebral irritation, 6 jaundice, 3 agranulocytosis, and 2 hæmorrhagic encephalitis. The majority of reactions appeared before the tenth day, were more often seen in primary syphilis, and appeared unrelated to previous Herxheimer reactions.

When treatment was resumed smaller doses of from one-fifth to one-half the previous dose, increasing to the maximum in from 2 to 5 days, were given in the mild cases, more severe cases received 1/100 of the dose, increasing to the maximum in 7 days. On resumption there was increased liability to both toxic erythema and

fever. A previous attack of fever had occurred in the cases of jaundice and agranulocytosis, and, though such an event was exceptional in those patients showing cerebral irritation and encephalitis, fever was usually noted as a prodromal or concurrent sign. Seventeen patients—4 with fever, 3 with toxic erythema, 8 with cerebral irritation, and 2 with agranulocytosis—received 2,3-dimercaptopropanol (BAL) by injection with apparently good results. One patient with hæmorrhagic encephalitis was given this drug by intubation with no demonstrable benefit.

The late onset of stomatitis probably prevented many cases with complications due to bismuth from being seen, but 5 severe cases were noted. There were also 2 instances of bismuth dermatitis, 5 of bismuth arthralgia, and 3 of bismuth "grippe". Four patients had albuminuria at the start, and in 2 of these bismuth was discontinued as this was increasing. In no case did albuminuria arise *de novo* during the course. R R Willcox

Six to Twelve Month Follow-up Results in Early Syphilis Treated by a Twenty-day Intensive Arseno-bismuth System. PILLSBURY, D M, and LOVEMAN, A B (1947) *Amer J Syph*, 31, 115

The results are reported of a follow-up lasting 6 months of 982 male patients treated for early syphilis by the "20-day" arsenic and bismuth regime (arsenoxide 20 mg per kilo body weight, divided into twenty daily doses, with eight injections, each of 0.2 g, of bismuth salicylate). Though the treatment was toxic there were no deaths, and of the first 775 patients 96.3% completed the course. Two facts are outstanding—serious reactions rarely occur during the first 5 days, and when they do they are almost invariably ushered in by fever. Of the 982 patients observed for 6 months, those with serum-negative primary syphilis gave 98.68% of negative serum reactions, those with serum-positive primary syphilis 95.1%, those with secondary syphilis 92.68%, and those with latent syphilis 76.32%, at 12 months in 258 cases the respective percentages for the first three groups were 97.56, 93.4, and 95.45. Approximately twice

as many unsatisfactory results were noted after 12 months as after 6 [a point of some importance as regards ultimate prognosis]. Serological relapses excluding the latent cases were commonest in the secondary group at 6 months (2.44%) but in the serum positive primary group at 12 months (5.66%). The cerebrospinal fluid of 785 patients was examined 6 or more months after treatment, and 6 (0.76%) were found positive. It is concluded that though the results are satisfactory this method of treatment is unjustifiable when penicillin is available. *T E Osmond*

**The Treatment of Early Syphilis by the Twenty-six-week Mapharsen bismuth Schedule** STERNBERG T H and LEIFER W (1947) *Amer J Syph* 31, 124

The '26-week' schedule for the treatment of early syphilis was adopted in the American Army early in 1942. It consisted of 40 injections of mapharsen (total 2.4 g) and 16 injections of bismuth (total 3.2 g) over a period of 26 weeks. The present article analyses the results in 3,000 patients, of whom 1,330 were in the serum-negative primary, 1,207 in the serum-positive primary and 463 in the secondary stage. Toxic reactions occurred in 63 patients and were mostly gastro-intestinal or pyrexial, there were no deaths, and in only 2 cases 1 of jaundice and 1 of dermatitis was it necessary to abandon arsenical therapy. (It is estimated that the expected mortality rate from this treatment is about 1 in 33,000 cases.) Patients were kept under observation for varying periods up to 3 years: the majority for 12 to 18 months. Serum-negative primary cases showed 98.25% satisfactory results, serum-positive primary 94.48% and secondary 84.34%. In the whole series only 18 (0.64%) showed pathological changes in the cerebrospinal fluid of these 4 were in group I, 4 in group II, and 10 in group III. Of these tests 91.1% were carried out during the first 24 months of observation. It is emphasized that the results do not represent the cure rate, with longer observations there might have been more relapses though on the other hand many persistently positive sera might have reverted to negative. *T E Osmond*

**Rapid Treatment of Prenatal Syphilis** OLANSKY, S, and BECK, R (1947) *Amer J Syph* 31, 51

Although congenital syphilis can be prevented, thousands of infected infants are born in the United States each year. The authors conclude that many syphilitic women do not receive adequate treatment during pregnancy, and believe this failure to be due to the fact that standard methods of antisyphilitic treatment take too long and are too difficult for the average patient. [In Britain congenital syphilis usually follows failure to diagnose maternal syphilis: the known syphilitic mother is usually co-operative and attends well for treatment throughout her pregnancy.] The authors have therefore studied intensive treatment methods in an attempt to prevent prenatal syphilis

and here report the results in 147 patients of whom 129 were studied for 3 months or longer after confinement. There were 128 live births, 5 abortions and 6 stillbirth. The 128 live infants were free from clinical signs of syphilis and only 1 had persistently positive serological evidence. In 2 cases of stillbirth the foetus showed no pathological evidence of syphilis, and in another 2 it was considered that the foetus had died before treatment was started. One of the abortions was considered to be traumatic and in another the foetus was thought to be dead before treatment was started.

The treatment schedules used were: (1) 1,200 mg mapharsen by slow intravenous drip over 5 or 8 days combined with 0.2 g bismuth subsalicylate weekly for 8 weeks. (2) 60 injections of 40,000 units of penicillin at 3-hourly intervals. (3) (a) 1 mg mapharsen per kilo body weight (maximum of 60 mg per dose) daily for 8 injections, 10,000 units of penicillin every 3 hours to 60 injections and 0.2 g bismuth subsalicylate on the first, fifth, and ninth days; (3) (b) injections of mapharsen on the first, third, fifth, seventh, and ninth days, 16,667 units of penicillin intramuscularly every 3 hours for 72 injections and 3 injections of 0.2 g bismuth subsalicylate. The findings justify the authors' conclusion that intensive antisyphilitic treatment even late in pregnancy results in a high proportion of non-syphilitic infants. *S M Laird*

**The Relative Toxicity and Therapeutic Activity in Experimental Syphilis of Bismuth Subsalsalicylate, Bismosol, and Biliposol** EAGLE, H (1946) *Amer J Syph* 30, 549

Three preparations representative of the water-soluble, the fat-soluble, and the insoluble types of bismuth compounds were used for this investigation. The author considers the bismuth preparations as a group to be from one half to one-third as active as mapharsen, and the safety zone between the effective and toxic doses to be from six to eight times greater than that provided by mapharsen. *V E Lloyd*

**The Rapid Treatment of Syphilis: Comparison of Results Using Five Treatment Methods** LEAVITT, H M (1947) *Amer J Syph* 31, 27

After treatment in hospital with one of five different methods 539 patients with syphilis were followed up for 6 or more months. The five treatment schedules were: (1) A daily injection of mapharsen (usually 0.06 g) for 6 days a week for twenty doses together with a weekly injection of 0.2 g bismuth subsalicylate. A further 8 weekly injections of bismuth after the patient left hospital were advised. (2) Daily injections of mapharsen 6 days a week up to a total of twenty-two injections, injection of 0.2 g bismuth subsalicylate on the first day of treatment and with every fifth injection of mapharsen. (3) Sixty injections of 40,000 units of penicillin at 3-hourly intervals (total 2,400,000 units in 7½ days). (4) A combined treatment—the 8-6-3 schedule—lasting 8 days comprising eight daily injections of mapharsen,



three injections of bismuth subsalicylate, and 10,000 units of penicillin 3-hourly for sixty injections (total 600,000) (5) A modification of (4), the "5-12-3" schedule, consisting of five injections of mapharsen in 9 days, three injections of bismuth subsalicylate, and seventy-two injections of 16,667 units of penicillin at 3-hourly intervals (total 1,200,000)

It was found that none of these five schedules was superior to long-term therapy or intensive arsenotherapy. Penicillin alone (3) was the safest, while the "8-6-3" schedule (4) produced two severe but non-fatal cases of arsenical encephalopathy. Further work is needed to determine the optimum combination of penicillin, arsenic, and bismuth required for the effective treatment of syphilis in its various stages.

[While the results are disappointing, they do indicate that the optimum treatment required must be more than that given in the schedules.]

S M Laird

**Injury to the Hæmopoietic System during Arsenotherapy for Syphilis Complicated by Diphtheria** (Beschadiging van de bloedbereidende organen tijdens arseno-benzolbehandeling van lues, welke door diphtherie is gecompliceerd) HOHMANN, W J (1946) *Ned Tijdschr Geneesk*, 90, 1562

After giving two case histories (one fatal) the author points to the danger of treating syphilis with heavy metals during or shortly after an attack of diphtheria, and recommends replacing them in such cases by penicillin.

R Salm

**Dichlorophenarsine Hydrochloride in the Treatment of Syphilis** BEERMAN, H, and WAMMOCK, V S (1947) *Amer J Syph*, 31, 150

Dichlorophenarsine hydrochloride is an almost colourless powder first described by the Germans in 1914. It is readily soluble in water, being converted into the arsenoxide and forming a yellowish solution which darkens on oxidation. The maximum standard dose is 0.068 g for males and 0.045 g for females. Early trials showed it to be ineffective in human syphilis, but success has since been obtained with buffered solutions and it is manufactured commercially as 'chlorarsen'.

In the present study 521 patients received from one to forty injections each (total 8,575) of a preparation of dichlorophenarsine hydrochloride buffered with four parts of sodium ascorbate. Sixty-two had primary, 116 secondary, and 343 later forms of syphilis. Three treatment schedules were used. To 310 patients the routine treatment was given, this consisted of continuous alternating courses of weekly injections of 0.03 to 0.068 g of the drug combined with 0.26 g of bismuth subsalicylate to a total of thirty arsenical and sixty bismuth injections. The doses and the duration of treatment in this schedule were increased by about one-quarter for the latter forms of syphilis. The so-called 26-week Army course was used for 189 patients and the Eagle and Hogan 12-week modified intensive course was employed for 22 patients.

Spirochaetes disappeared as quickly, healing of lesions was as satisfactory, and serological reversal was as rapid as with "mapharsen". There were only 3 cases of serological and no case of infectious relapse. The total absence of the latter is attributed to the incomplete follow-up, information in respect of 206 of the 521 patients being for periods under 6 months.

Seventy-one patients (13.6%) had mild reactions. 52 had nausea and vomiting, 2 nausea and diarrhoea, 1 chills and abdominal pain, 1 abdominal pain alone, 2 dizziness, 4 headache, 2 chills and fever, and 1 each pain in the back, rash, and nitritoid crisis. [The remainder are not listed.] Three had Herxheimer reactions. Thirty-eight patients were later given the drug without adjuvants and there was no reaction, 6 more received the drug with benzocaine lozenges and 8 with atropine before injection, there were no reactions. While some patients intolerant of the drug subsequently received neoarsphenamine without reaction, 11 patients previously showing reactions to neoarsphenamine tolerated dichlorophenarsine hydrochloride. It is concluded that the drug is a safe and effective arsenical suitable for use instead of mapharsen.

R R Willcox

**Penicillin in the Treatment of Experimental Syphilis of Rabbits** I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil-Beeswax by Intramuscular Injection. KOLMER, J A (1947) *Arch Derm Syph*, Chicago, 55, 741

Rabbit experiments were performed with two specimens of penicillin of a potency of 544 and 1,624 units per mg, and of a G content of 88 and 92% respectively. These penicillins, dissolved in isotonic saline solution, were compared in their effect on rabbit syphilis with the same penicillins suspended in a mixture of arachis oil and 3% beeswax at a concentration of 10,000 units per ml. All rabbits were inoculated intratesticularly with the Nichols strain of *Treponema pallidum* and all developed orchitis positive on dark-field examination 5 to 6 weeks later. Treatment was then instituted and dark-field examinations performed daily for 3 days and thereafter weekly for 10 weeks, at the end of this time the popliteal lymph nodes were inoculated into the testicles of fresh animals and these were observed for a minimum of 4 months.

Two rabbits were each given single injections of both penicillins in saline solution in doses of 10,000, 30,000, and 100,000 units per kilo body weight. Though preliminary dark-field tests became negative, all 12 rabbits later relapsed and showed positive lymph node transfers. With the same doses of penicillin in oil-wax, however, a cure was obtained in 3 out of 4 receiving a single injection of 10,000 units per kilo and in all 8 receiving the larger amounts.

When injections were given daily multiple doses of 1,000, 5,000, and 25,000 units per kilo were employed once daily for 8 days. With saline solution, temporary improvement with later

relapse was noted in all 4 on the lowest dose and in 3 with the total dose of 40 000 units, no improvement was noted with the total dose of 200 000 units. With penicillin in oil beeswax 3 out of 4 rabbits were cured by the lowest dose and all by greater doses. With multiple injections of the same doses given twice daily over 8 days 3 out of 4 rabbits responded to the lowest doses of saline solution and all to the higher doses while with penicillin in oil beeswax all 12 animals were cured.

Thus the results with penicillin in oil beeswax in rabbit syphilis show a decided improvement on those with penicillin in saline solution.

R R Willcox

**Relation of the Size of the Inoculum and the Age of the Infection to the Curative Dose of Penicillin in Experimental Syphilis, with Particular Reference to the Feasibility of its Prophylactic Use**  
EAGLE, H., MAGNUSON, H. J. and FLEISCHMAN, R. (1947) *J. exp. Med.*, 75, 423

Material used in this study consisted of the Nichols strain of *Treponema pallidum* passaged intratesticularly. Inocula were obtained by emulsification of rabbit testicular chancre in 50% rabbit serum and dilution to obtain concentrations of  $10^6$ ,  $10^4$ , and  $10^2$  organisms per ml. 0.2 ml of the appropriate dilution being injected intracutaneously or intratesticularly. Penicillin in one single intramuscular dose of a suspension in oil and beeswax, was administered 4 hours 4 days or 2 weeks after inoculation. At each of these intervals groups of 4 to 11 rabbits were given increasing doses to determine the abortive dose of penicillin required. This latter dose was compared with that necessary to cure animals treated 6 weeks after inoculation and after a lesion had developed. Administration of relatively small doses of penicillin 4 days after inoculation aborted the disease, the preventive dose (PD) varied with the size of inoculum and with the age of the infection. Thus in animals inoculated with 20, 2 000, and 200 000 spirochaetes and treated 4 days later 200, 500 and 3 500 units per kilo, respectively, were needed to protect half the animals and the corresponding PD90 dosages were 500, 2 000, and 16 000 units per kilo. With a fixed intratesticular inoculum the PD50 of penicillin remained at a constant level for 4 days. By the end of the second week more than seven times the dosage was required while by the sixth week, after the appearance of the chancre more than thirty times the amount was necessary to produce the same results.

The authors consider that administration of penicillin in one single intramuscular dose shortly after contact might prove a successful form of prophylaxis in human infection. In man and rabbit renal clearance of penicillins F, G and X is maximal, the blood level falls at essentially the same rate and after intramuscular inoculation there are comparable rates of absorption. Equal dosages per kilo in both species should therefore, produce similar results on the spirochaete. Thus

in the average adult a single intramuscular injection of 15 000 units in peanut oil and beeswax after say 4 days exposure might effectively abort infection. Even oral administration of three to five times this dose should prove effective. This suggests a new approach to the prophylaxis of syphilis, for if the spirochaete multiplies as slowly in man as it does in the rabbit a single dose of penicillin orally or intramuscularly should even abort the infection if it is given days after exposure.  
M. M. Buchanan

**Effect of Penicillin on Serology of Late and Latent Syphilis (A Study of 120 Cases Followed for Six Months or More)** WILLCOX, R. R. (1947) *Lancet*, 2, 8

The author studied the effect of penicillin on the serology of 120 military personnel treated at an army hospital for congenital latent, and late syphilis. The comparatively short time of 6 months observation or more was sufficient to detect the trend of the early pathological changes in response to penicillin. A qualitative Wassermann and a quantitative Kahn test were carried out on the blood serum once a month for the first 6 months, quarterly for the following year and 6-monthly for a further year. The cerebrospinal fluid was examined before penicillin was given and again after 6 months. It will again be examined after 2 years.

The cases were divided into four clinical groups: congenital syphilis 25, early latent syphilis (known infection within 5 years) 33, latent syphilis (duration unknown) 34, and late symptomatic syphilis 28. Serological results are ingeniously arranged into four groups of varying stability: (1) low declining titre, (2) high fluctuating titre, (3) high fixed titre (completely resistant to previous treatment) and (4) high titre of unknown stability (not previously treated). Groups 1 and 2, both with fluctuating titres after previous treatment responded most favourably (74.2 and 94.4% respectively) while group 3 with fixed titre to arsenic and bismuth gave little evidence of further improvement (16.1%). Group 4 a mixture of the other groups showed indifferent success (27.5%). The results in cases with an initially low titre were better after 6 months but the improvement was not maintained and an appreciable number of patients relapsed. The improvement continued for 9 or 12 months in the cases with a high fluctuating titre. Latent syphilis of recent origin responded most, while late syphilis and congenital syphilis responded least. The cerebrospinal fluid was abnormal in 18 cases, only 9 cases had improved of the 15 examined 6 months later and only 3 among the 9 showed similar improvement in the blood. In this small series the findings in the blood and in the cerebrospinal fluid were not parallel.

As the author states the analysis is confused because many patients had been treated with arsenic and bismuth before penicillin was given. Again some patients were given arsenic and bismuth after penicillin failure in these cases however would imply failure after penicillin alone.

Patients had a total dosage of 2,400,000, 4,000,000, and 4,800,000 units of commercial penicillin in aqueous solution in 3-hourly injections of 40,000 units. Six of the 25 congenital syphilitic patients improved. All the 33 cases with early latent syphilis had had arsenic and bismuth previously, 26 (78.8%) improved. As would be expected, results were less satisfactory in patients with latent syphilis of unknown duration: 16 out of 34 responded. At the end of 6 months only 8 (28.6%) of the 28 patients with late, mostly gummatous, syphilis had improved.

[The marked difference in the total dosage of penicillin in the three schedules of treatment must affect the value of the comparative figures in this study; accurate comparisons can hardly be made, since the dosage received by the various categories of patients is omitted.] — T. Anwyl-Davies

**The Clinical, Radiologic, and Pathologic Aspects of Late Pulmonary Syphilis—Effects of Penicillin Therapy.** KULCHAR, G. V., and WINDHOLZ, F. (1947) *Amer J Syph*, 31, 166

Four cases are described of the extremely rare late pulmonary manifestations of syphilis, 1 of which was treated successfully with penicillin. Necropsy figures as to incidence have varied from 1 in 3,000 to 12 in 1,500. It is suggested that late pulmonary syphilis may be more common than is realized. Recorded cases have shown it to be nearly twice as common in males as females and to have an age incidence between 2 and 98 years. Most cases were diagnosed 5 or more years after infection (10 to 11 years was not uncommon). It is not infrequently associated with cardiovascular syphilis, and some workers have suggested that the pulmonary process is an extension of earlier disease in the mediastinum.

The disease may be asymptomatic or may appear as a chronic chest lesion with chronic cough and sputum, sometimes blood-stained, associated with dyspnoea, loss of weight, and sometimes night sweats, pain in the chest, and even severe haemoptysis. Before syphilis of the lung can be diagnosed the commoner pulmonary lesions of pneumonia, neoplasm, fungus infections, and tuberculosis must be excluded, and a history of previous syphilis (if possible) and a positive serological reaction obtained. The lesion should show clinical and radiological improvement with antisymphilitic treatment. The disease may occur as an acute syphilitic bronchopneumonia, a chronic interstitial syphilitic pneumonia, a syphilitic bronchiectasis, or a gumma. From the clinical standpoint no differentiation of these types is possible. The radiological appearances are not specific, though rounded shadows like tumour masses are sometimes seen in the lower lung fields and, if interstitial fibrosis predominates, radiating parenchymal markings are observed in the hilar region. The condition should be considered whenever bizarre lung films are seen. It is very rare for *Treponema pallidum* to be recovered from the lesions.

In the first case described a white man aged 73, had had a penile sore at the age of 21. He was admitted to hospital with syphilitic aortitis, and

radiographs showed involvement of the right lower lung field. The second patient, a woman aged 56 with a gumma of the neck, had no symptoms but a hilar shadow which disappeared after antisymphilitic treatment. In the third case, that of a man of 33 years, a hilar shadow was also seen in the radiograph. Treatment was purposely withheld for 3 months, no change being observed; the lesion subsequently resolved under treatment. In the fourth patient, a man of 29, there was a strongly positive serological reaction associated with periostitis of the left femur and the first left metacarpal bone: a radiograph showed a sharply outlined rounded density 1 in in diameter in the sub-pleural region of the left lower lobe. After 2,400,000 units of penicillin had been administered (40,000 units every 3 hours for 7½ days) the radiological findings became almost normal within a month and remained so 5 months later. — R. R. Willcox

**Penicillin in the Treatment of Neurosyphilis. A Study of One Hundred Cases Followed Twelve Months or More.** ROSE, A. S., and SOLOMON, H. C. (1947) *J Amer med Ass*, 133, 5

The authors treated 236 neurosyphilitic patients with 3,000,000 units of penicillin between Feb 1944, and April, 1946, and report the results in 100 who have been followed for a year or more. When fever therapy was also used the amount was about half that usually administered. The following are some of the results obtained: Penicillin plus malaria caused "improvement" in 66% of patients, penicillin fever with cabinet, 52%, and penicillin alone, 58%. Of the 100 patients 36 required re-treatment; it made little difference whether the penicillin was given 2-, 3-, or 4-hourly or whether it extended over 5, 7½, 10, or 15 days, though the authors state that the 15-day patients less often required re-treatment. Of 75 patients with general paralysis of the insane treated by one or other of the three methods, 69% were improved and 38% required re-treatment. As regards the spinal fluid, the cells tended to return to normal in 3 to 6 months, the protein in 6 to 9 months, and the Wassermann reaction more slowly, only 11 patients giving negative reactions. There were 12 deaths among the 236 patients, 6 of which were due to G. P. I. and the rest to causes other than syphilis; in 1 case of G. P. I. it was thought that penicillin contributed to the fatal result. It is concluded that the amount of treatment employed was inadequate for late symptomatic syphilis, and the amount of penicillin has now been doubled.

[The Wassermann reaction is stated to have been "carried out in six dilutions of spinal fluid as follows: 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 c cm. These are not dilutions but absolute quantities.]

— T. E. Osmond

**Sulphonamide Therapy and Serological Reactions of Syphilis.** (Terapia sulfamidica e reazioni sierologiche della lue.) RENATO, R. (1947) *G. Batt. Immun.*, 36, 3

The question of false positive serological reactions after sulphonamide therapy was investi-

gated in 76 patients suffering from a variety of general medical, skin, and gonococcal affections. So far as could be determined, they had not had syphilis, and serological reactions were negative in all before treatment. The patients received sulphanilamide, sulphapyridine, sulphathiazole, or methyl sulphathiazole, usually by mouth. The four serological reactions (Wassermann Kahn, Meinicke, Sachs-Witebsky) repeated from 2 to 10 days after beginning treatment became positive in 16 patients who had received from 12 to 90 g. of sulphonamide. In 2 patients the reactions remained slightly positive 2 months after stopping sulphonamide therapy but later reverted to normal, in the other 14 patients the reactions became negative after 10 days to 2 months. The flocculation reactions were more often positive than the Wassermann reaction and all positive reactions were usually weak. After the serological reactions had returned to normal, provocative doses of bismuth and arsenobenzene were given, with negative results in all cases.

The author discusses the theoretical significance of these observations, particularly in relation to a possible disturbance of liver function by sulphonamide therapy, producing changes in serum proteins. The false positive reactions are weak and transient and should give rise to no diagnostic difficulty provided the tests are repeated when found positive in patients who have recently received sulphonamide therapy.

L P R Fourman

### SYPHILIS (Pathology)

The Antigenic Specificity of Syphilitic Antibody Globulin. HENRIKSEN, S D (1947) *J Immunol* 55, 153

The author reports investigations designed to study the immunizing properties of syphilitic antibody when injected into animals, and to compare the reactions of the immune sera thus produced to the homologous antigen and to various normal serum proteins.

Strongly positive syphilitic serum was flocculated with the antigen as described by Wadsworth and Brown (*J Immunol*, 1936 31, 155), 0.5 to 1 volume of antigen per volume of inactivated serum proving experimentally to be the maximal flocculating dose, the floccules were centrifuged and washed four times with 10 to 15 ml. quantities of saline. The resulting dense suspensions of washed floccules were used for immunization. Rabbits were injected intravenously 2 to 3 times weekly for 3 to 4 weeks and bled 1 week after the last injection. Complement fixation and precipitation tests were performed before and after absorption with the following antigens: strongly positive inactivated syphilitic serum, pooled inactivated normal serum, Wassermann antigen prepared by Kolmer's method, serum globulin and serum albumin water insoluble and water-soluble globulins and purified syphilitic antibody.

The results showed that when such washed floccules are injected into rabbits two different antibodies are produced which can be differentiated from each other by absorption. One is directed

against the lipid antigens of the heart extract and is of a similar specificity to the syphilitic antibody and the other is directed against the syphilitic antibody which is combined with the lipid antigen in the floccules. The specificity of the latter antibody is not characteristic of the specific reactive groupings of the exciting antigen as it reacts just as well with normal human serum as with strongly Wassermann-positive serum. A comparison of the reactivity of the various protein fractions with the immune serum showed that practically all the reactive antigenic material is present in the globulin fraction. Within this fraction the reactive antigen was mainly concentrated in the water insoluble portion. The author concludes that the specificity of the syphilitic antibody appears to be the same as that of certain normal serum globulins. The syphilitic antibody seems to be more closely related to the euglobulin than to the pseudoglobulin fraction.

A Henderson Beggs

Experimental Syphilis. Qualitative and Quantitative Studies of Reaction in Normal and Syphilitic Rabbits. SHERWOOD, N P and COLLINS C (1946) *Amer J Path*, 30, 571

The standard and quantitative Kahn, Kolmer and Kline tests and the differential temperature technique were employed in this inquiry. A group of 23 rabbits served as a control. The second group studied as normals for some weeks, were then inoculated intratesticularly with *Treponema pallidum*, and all were tested at weekly intervals for from 7 to 51 weeks. All 23 normal rabbits showed some type of immune body at one time or another, the titre of the immune body was low and variable. The 52 inoculated animals were observed for periods of up to 51 weeks. Only 2 showed the general biological type of reaction throughout. The remainder showed various combinations of two or all three types of antigen. No correlation was found between their titre and type of immune body present in syphilitic rabbits. The differential temperature Kahn verification test did not show a quantitative difference between the immune body of normal and of syphilitic animals.

V E Lloyd

Transmission of Experimental Syphilis from Mouse to Mouse—Absence of *Spirochaeta pallida* and of Pathologic Changes in Presence of Successful Inoculation. WILLIAMS, U J (1947) *Amer J Syph*, 31, 109

The testicles of rabbits infected with the Nichols strain of *S. pallida* were ground up and injected into the brain and peritoneal cavity of mice. Brain and organ emulsions of the mice infected a rabbit after 60 days. After a second, third, and fourth mouse passage the organs but not the brains were found to be infective. A fifth passage was attempted but the rabbit showed no clinical evidence of syphilis though it developed a Kahn reaction of 80 units and proved resistant to inoculation at a later date. The intervals of time between inoculation of the rabbits with mouse material and the development of syphilitic lesions

were 27, 58, 48, and 81 days respectively, suggesting that the spirochaetes tended to diminish in virulence with successive transfers. In none of the mouse organs could spirochaetes be demonstrated by dark-ground examination staining with hæmatoxylin-eosin, or the Warthin-Starry silver impregnation method. This suggests that the spirochaetes in the mice had assumed an infra-visible or granular form. It is interesting to note that the organs (spleens and gonads) of the mice were capable of carrying the infection much longer than the brains.

T E Osmond

**False Positive Tests for Syphilis. A Study of their Incidence in Sporozoite-induced Vivax Malaria**  
REIN, C R, and KENT, J F (1947) *J Amer med Ass*, 133, 1001

Ninety male volunteers with no evidence of syphilis were inoculated by mosquito bite with sporozoites of vivax malaria. Specimens of serum were obtained from each patient before inoculation, at daily intervals during attacks, two or three times weekly after attacks, and at minimal weekly intervals for a total period of 18 months. The specimens were subjected to several tests for syphilis, including the standard Kahn, the Hinton flocculation, the Kline diagnostic and the Kline exclusion, the Mazzini and the Boerner-Jones-Lukens micro-flocculation tests, and a newly developed micro-flocculation test with a cardiolipin antigen (Rein and Bössak). 44,958 tests were carried out on a total of 7,493 sera.

Of the 90 patients, 57% developed false-positive reactions with one or more tests, but the Hinton gave only doubtful reactions over a 2-day period, and Rein and Bössak's remained negative throughout. The standard Kahn and Kline exclusion tests gave the strongest non-specific reactions. Most of the sera were subjected to several complement fixation tests including the Kolmer-Wassermann. About the same number of false-positive reactions were obtained as with the more usual flocculation tests.

G L M McElligott

**The Weltmann Serum Coagulation Reaction in Syphilis**  
CALLAWAY, J L (1947) *Amer J Syph*, 31, 216

The Weltmann serum coagulation reaction is a non-specific empirical test, comparable with the erythrocyte sedimentation rate, giving consistent values in the healthy and a definite range of deviation in certain pathological states such as acute infections. It is apparently unaffected by dehydration, acidosis, alkalosis, anaemia, or allergic states, and, while it bears no relation to the albumin-globulin ratio, there is a lower reading when the  $\alpha$ -globulin level is high and vice versa.

The test is performed by mixing in ten tubes 0.05 ml of the blood serum to be tested with 2.5 ml of serial dilutions of from 0.1 to 0.01 ml of 10% calcium chloride solution. The tubes are placed in a boiling water bath for 15 minutes before the number of tubes in which coagulation has occurred is ascertained. The normal is six, and a shift to the left is said to have occurred if

less, and to the right if more, are involved. Generally speaking, inflammations and infections cause a shift to the left, and fibrosis and degenerations to the right.

The serum of 610 syphilitic persons was examined, 132 had primary, 148 secondary, 162 latent, 34 congenital, and 21 cardiovascular syphilis, while 113 had neurosyphilis. The average readings for all groups but two were in the range 7.0 to 7.4, the reading for neurosyphilis was 6.3 and for prenatal syphilis 5.7. Of patients with early syphilis, 32 showed no appreciable change in the reaction after treatment for 6 months with arsenic and bismuth, as did 18 of the cases of neurosyphilis treated with fever, and 40 given penicillin. It is concluded that while a slight shift to the right can be observed in all forms of syphilis except congenital, the reaction is non-specific.

R R Willcox

### GONORRHOEA (Therapeutic)

**Arthritis in the Mediterranean Theatre of Operations. III Clinical Description of Infectious and Other Types of Arthritis**  
SHORT, C L (1947) *New Engl J Med*, 236, 468

Infective types of joint disease in the Mediterranean theatre are reviewed. At the Twelfth General Hospital 20 out of 173 cases of dysentery developed arthritis, and of these 10 also developed urethritis or conjunctivitis or both (Reiter's syndrome). The author suggests that the dysentery merely provided a portal of entry for the causative agent of Reiter's syndrome, and he even regards the arthritis following dysentery as due to a secondary invader. He finds support for this view in the fact that neither the arthritis nor the urethritis reacts to chemotherapy, to which dysentery reacts readily.

Gonococcal arthritis was treated by sulphathiazole combined with intra-articular penicillin. Cases which failed to respond to this treatment are regarded as being cases of rheumatoid arthritis rather than of true gonococcal arthritis. Meningococcal arthritis was found to be little affected by chemotherapy or penicillin, but all cases recovered.

H F Turner

### OTHER VENEREAL DISEASE CONDITIONS

**Rickettsial Forms in Pus from Lymphogranuloma Venereum**  
(Sul reperto di forme Rickettsiose nel pus poradenitico)  
D'IGNAZIO, C, and CODELEONCINI, E (1946) *Boll Soc Ital Med Ig trop*, 6, 243

By inoculating pus from lymphogranuloma venereum anally into lice, following Weigl's technique for infecting lice with rickettsiae, the author claims to have obtained growth of rickettsial forms from the virus of lymphogranuloma venereum.

[Insufficient steps appear to have been taken to exclude infection of the lice with *Rickettsiae* type Rocha Lima, which are common commensals in the intestine of lice in Africa.]

G M Findlay

Streptomycin in the Therapy of Granuloma Inguinale GREENBLATT R B LUPPERMAN H S, and DIENST R B (1947) *Proc Soc exp Biol N Y* 64, 389

Antimonial preparations are well established in the treatment of granuloma inguinale but the lesions may recur even if local therapy is also employed. Penicillin seems of little value. Streptomycin has proved so effective in the treatment of 23 cases that the authors consider a preliminary report justified. The condition was diagnosed by the finding of Donovan bodies either in smears or in biopsy sections. No other drug was used. Doses ranged from 0.3 g to 1 g daily. Treatment was given every 4 hours and lasted from 6 to 46 days. Healing was usually centripetal and Donovan bodies could not be demonstrated in smears taken from 5 to 9 days after treatment had started. The moist ulcerated areas around the scrotum took longest to heal but were ultimately covered by scar tissue.

Toxic reactions occurred in 2 patients after 10 days treatment. One developed a maculopapular rash on the limbs and lower jaw with a fine vesicular eruption and oedema of the lips; none of the lesions responded to benadryl (100 mg daily). The other patient complained of a mild burning of the conjunctiva, which did not reappear when the drug was renewed after a short pause.

Relapses may occur even when as much as 28 g. has been given. In spite of this streptomycin is undoubtedly the most effective agent known today for treating granuloma inguinale.

T E C Early

## PUBLIC HEALTH

Ten Years of Premarital Blood Test Law TALBOT H P (1947) *M J Offr* 77 55

This article describes the procedure in obtaining a premarital blood test certificate and tabulate the numerical result of the application of this law in Connecticut. The objectives of the law are (1) to prevent an individual with syphilis from infecting the marital partner (2) to prevent congenital syphilis and (3) to uncover syphilis so that proper treatment may be given. Blood samples can be taken by any licensed physician and sent for test to an approved laboratory. If the result is satisfactory a certificate is signed by the physician and by the applicant in his presence. This is valid for 40 days and must be produced to obtain a marriage licence. The physician does not sign if the applicant is found to have syphilis in a communicable stage. The disease is not usually infectious to the marital partner after 4 or 5 years even in the absence of treatment. A woman with untreated syphilis is always potentially dangerous to her offspring. The rate of positive individuals varied in the 10 years between 9.7 and 19.1 per thousand. A great many were unaware that they were infected, and often the physician was able to sign the certificate as the disease was not in a communicable form.

[The great value of premarital blood tests in unmasking syphilis is well illustrated]

James Marshall

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